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BRITISH MEDICAL JOURNAL

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MODE OF ACTION OF SOME TOXIC SUBSTANCES

WITH SPECIAL REFERENCE TO THE EFFECTS OF PROLONGED EXPOSURE*

BY

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In the first Ernestine Henry lecture, entitled "Devices to Protect the Worker," Dr. Donald Hunter said: "Medical examination with adequate laboratory aids should detect intoxication before disability occurs." If it be permitted to include studies in the experimental laboratory among the "aids" referred to by Dr. Hunter then what follows may be regarded as coming within the terms upon which this lectureship was established.

In many occupations, both old and new, men and women are brought into contact with all kinds of materials which in one way or another are capable of behaving as poisons. As technology advances not only certain groups of industrial workers but also the general public meet with an increasing number of chemical substances, some of which may have only recently been created. Past experience, however, has indicated that it may take many years before the incidence of a disease is recognized as having a relation to exposure to a chemical. It is therefore not surprising that voices have been raised in alarm at the possible threat to health that may be associated with prolonged exposure to new substances. It would probably be fair to say that much more alarm has usually been expressed on behalf of the public who may come in contact with traces of a new material than on behalf of the smaller groups who may, by their occupations, come into much more intimate contact with much greater amounts. In this context it is worth bearing in mind the general epidemiological principle that the larger the dose the more likely is an effect to be seen.

If it is suspected that a chemical might have a delayed toxic effect or an effect that is only obvious after prolonged exposure to the material, a search for any reaction should begin among the appropriate sections of the population. For example, alarm is not infrequently expressed that the traces of some of the new insecticides which may find their way into our food could eventually prove injurious to the health of the consumer in a manner usually not specified. Some years ago the World Health Organization tried to find out from several large manufacturers what, if any, experience of illness they had had among those who made such insecticides. The replies made it clear that the large responsible manufacturer of a poisonous new product protects his employees from any significant exposure to it. It therefore seemed unlikely that much would be learned from a long-sustained study of such small specialized working populations.

As in the case of many other new chemicals, the people who are more likely to be exposed seriously to new insecticides are those who use them. Clearly it is going to be very much more difficult to conduct an epidemiological surveillance lasting many years over groups of local labourers in some tropical country who are exposed to an insecticide year after year in the course of a malaria eradication campaign, or to small groups of men in a number of engineering shops heavily exposed to some new degreasing solvent. The value of proper studies on man in order to gain knowledge of the potential hazards which poisonous materials may present to him cannot be overestimated. However, the difficulties and duration of any searches for the effects of prolonged exposure underline the need for, and indeed the desirability of, discovering other criteria that may enable one to predict with reasonable certainty whether or not a new chemical is likely to prove dangerous to man.

The alternative criteria which first spring to mind are those that can be obtained from studies of the effect of a chemical on biological systems other than man himself. An attempt will be made to consider this problem in a general way with a few illustrations from among many substances that may present a hazard to those who make or use them. It is important to try to understand how far studies in the experimental laboratory may make it possible to draw reasonable conclusions about the probable effects of new substances upon man. Particular consideration will be given to the possible effects from prolonged exposure because from every point of view these are the most difficult to determine.

Maximum Allowable Concentrations

A poisonous substance given either as a single dose or in repeated doses over a short period produces a distinct and recognizable effect upon function and structure. Where prolonged exposure has to be incurred the practice of good industrial hygiene will create conditions in which the amounts absorbed by the people using the toxic product will not produce the signs and symptoms of poisoning characteristic for that material when received in larger amounts over a shorter period. Estimates of what are thought to be innocuous dose levels to which it may be safe to allow exposure for limited periods, usually eight hours daily for five days a week, are embodied in the figures for maximum allowable concentrations (M.A.C.). These, of course, apply only to those substances that are absorbed from the working atmosphere via the respiratory route.

By analysis of workshop air it is possible to get some idea to what a group is exposed, though this may provide

*Ernestine Henry Lecture delivered to the Royal College of Physicians of London on June 20, 1961.

only a very rough approximation to the actual exposure where many different operations are carried out in a workshop. It is not normally possible to estimate the dose received by the percutaneous route of absorption. Special studies of this kind have been made in certain operations, such as those in which insecticide sprays have been applied to large numbers of houses in disease eradication programmes. Despite the apparent hazard from the inhalation of the spray droplets in these confined spaces the contamination of the exposed skin by droplets was found to be 200 times as great as from that which was inhaled (Wolfe *et al.*, 1959). Many solids as well as liquids can penetrate the intact skin, so that it is necessary to bear in mind that the factory air may only be one of the routes of absorption. The dose of chemical a man actually receives during a working day may be far greater than that which he actually inhales. The importance of skin absorption and ingestion will naturally vary greatly with the type of operation and the extent to which the worker is physically contaminated by the substances.

Figures for the M.A.C. of gases, fumes, and dusts that may present a hazard in industry are issued by the United States Industrial Hygiene Association and have been available for years. These figures have recently been adopted by the Factory Inspectorate in this country, and very similar figures are used in several European countries. A set of figures in which the safe levels of many of the same materials are very much smaller is issued by the U.S.S.R. (Elkins, 1961). The reason for the discrepancy between these recommended levels is discussed later, but it is as well to note that these higher standards are apparently to be applied only to new factories within the U.S.S.R. The general population may come into contact with other substances, such as many of those now added to manufactured and processed food, many of which have no demonstrable toxic effect when given in single doses. This does not prevent some people from expressing alarm that ill effects may eventually appear if small quantities of such materials are taken over very long periods.

Study of Toxic Action

For the experimental toxicologist to be able to provide answers to the questions concerning the quantity of a poison that may be ingested safely for an indefinite period, he needs to undertake a detailed analysis of the mode of action of the poison. To satisfy some of those who worry whether an inert material will remain harmless however long it is ingested may be psychologically impossible. To assure himself, however, that the substance is truly inert in the doses envisaged calls again for a study of its behaviour in the animal body so that the reason why it does not harm the organism can be explained in scientifically satisfactory terms.

How can a study of the toxic actions of certain substances be interpreted in such a way as to act as a guide for defining probabilities about the effects on man from a prolonged exposure ? The most obvious place to begin is the point of contact between the animal and the chemical. However, despite its tremendous importance in occupational medicine, damage to the skin will not be considered here. Local effects on the mouth or alimentary tract do not loom large in this field, and, like the eyes, these seem to be sensitive areas where unpleasant contact is readily noticed and avoided. The lower respiratory tract appears, however, to be different. There is much interest in the field of atmospheric pollution and its possible relation to disease, especially in the elderly and longest exposed.

Irritant Gases

Sulphur dioxide is one of the irritant gases that have been studied in the laboratory. The M.A.C. for industrial exposure is 5 p.p.m. Amdur *et al.* (1953) claimed that an exposure to 1–8 p.p.m. for only 30 minutes could produce changes in the respiratory pattern of healthy human subjects, but Lawther (1955) was unable to repeat their observations. However, Amdur (1958–9) has found that 2.6 p.p.m. for an hour will increase the airway resistance of the guinea-pig. Dalhamn (1956) has described some interesting changes in the bronchial mucosa of rats exposed to 10 p.p.m. of sulphur dioxide for 10 weeks. Both the quantity and quality of the mucous secretions changed and there was multiplication of the mucus-secreting cells in the depth of the bronchial epithelium. These changes had regressed little, if at all, in animals examined four weeks after exposure to sulphur dioxide had ceased. One characteristic feature of the bronchial mucosa in chronic bronchitis in man is an increase in the numbers of mucus-secreting glands and goblet cells (Reid, 1960). Despite the changes wrought in the mucosa of these rats the cilia, though less effective in moving the altered mucus, remained as lively as ever, beating 1,200–1,300 times a minute.

These interesting studies seem not to have been extended, despite the indications they provided of the action of an irritant gas on the respiratory mucosa. Other poisonous gases react first with the alveolar lining of the lungs, and over-exposure results in pulmonary oedema. A method has been described by Long and Hatch (1961) in which the efficiency of the absorption of ^{14}C-labelled carbon monoxide through the lungs can be studied in intact animals. It is perhaps rather disquieting to note that an effect on the absorption of carbon monoxide, which probably reflects some change in the alveolar lining of the lungs, could be detected in rats which had been exposed for only 30 minutes to 1 p.p.m. of phosgene. This is the concentration which is thought to be safe in a working environment. If man is as sensitive as the rat to phosgene, such a concentration can hardly be called an ineffective level. With this new technique the effects of other irritant gases against more species could be studied, and these first observations indicate an urgent need for more work on these lines to be undertaken.

Pattle (1958) described an interesting material which coated the bubbles expressed from mammalian lung. He deduced that the presence of this material as a monomolecular layer prevented mammals from drowning in their plasma abstracted from the blood by the capillary attraction exerted by the small air-filled alveolar spaces. That this lipoprotein (Pattle and Thomas, 1961) has the exact role in the lung which Pattle assigned it has been questioned (Mead, 1961). Nevertheless the action of lung irritants upon its production and behaviour seems worthy of further study, particularly in relation to the effects of repeated exposure. For example, it has been shown that a small dose of ozone will protect mice for many days from the pulmonary oedema that results from exposure to higher concentrations of this gas (Stockinger *et al.*, 1956 ; Matzen, 1957).

For a country in which respiratory disease takes such an annual toll in death and disability perhaps more could be done to study the intimate reactions between toxic and irritating materials on the delicate and vital structures of the respiratory tract. No one is certainly in a position to be anything but cautious and pessimistic in predicting the likely effects of prolonged exposure to toxic materials which act as primary irritants on the lungs.

The effects of substances after they have been absorbed will now be considered. Before leaving the lungs the problems presented by dust are briefly discussed. Any particles in the inhaled air which are below a certain size—about 7 microns of unit density—will reach the lungs. Unless they are very small—less than 0.1 micron—most of these particles will be retained. A mechanism for clearing the lungs of inhaled particles exists, but the colour of the lungs of any healthy middle-aged city dweller demonstrates that this mechanism is inadequate to keep the lungs free of inhaled soot even for those who live in what might be regarded as a normal environment. Whenever dust is inhaled in excessive quantities it can be assumed that substantial amounts will be retained within the phagocytic cells in the pulmonary tissues.

The Pneumoconioses

Of the pneumoconioses, silicosis is the best known, the most widespread, and probably the most serious. Simple experiments indicate that silica has a toxic effect upon cells anywhere in the body, so it is not surprising that serious tissue injury develops round deposited silica. However, there is no simple explanation of why silica is toxic or why silicosis is such a serious disease. It is by no means easy to follow the various arguments for and against the solubility theory of silicosis (Holt, 1957). Alternative and complex hypotheses presumably reflect some difficulty in accepting the idea that silica particles are toxic because the toxic silicon dioxide gradually leaches out of them into cells containing or surrounding the particles. It has been suggested that silicosis is a disease in which the development of some degree of auto-immunity plays a part (Vigliani and Pernis, 1959). The antigen suggested is a polysaccharide believed to be liberated from macrophages killed by the silica which they have ingested. If this notion of auto-immunity comes to gain general acceptance as an explanation of the lesions of the pneumoconioses, the present state of knowledge will not permit very much use being made of animal experiments for the purpose of predicting whether diseases of this type will follow the inhalation of a new dust.

Indeed, the limitation of animal studies in this connexion had already been made obvious by the problems presented by berylliosis. The serious nature of the chronic and progressive form of this disease in man was recognized soon after the second world war. As an occupational disease it disobeys some of the usual rules, particularly the one in which the severity of the disease is related to the extent of exposure to the noxious material. While there is no doubt about the toxicity of the beryllium ion, and while there is some histochemical evidence that beryllium ions leach into the tissues from deposits of insoluble beryllium oxide, there seems equally little doubt that the element of hypersensitivity plays an important part in affecting the course of the disease in some, if not all, the victims (Sterner and Eisenbud, 1951). Nevertheless, it has proved impossible to demonstrate hypersensitivity to beryllium or silica in guinea-pigs using techniques that are effective with other materials (Collet *et al.*, 1961). If auto-immune phenomena play a part in both silicosis and berylliosis the precise mechanism must be quite different if one may judge by epidemiological experience of the two diseases, and it would seem quite misleading to group the conditions together (Gross, 1960).

When a completely inert dust is inhaled in large quantities dramatic changes in the radiograph of the chest may be seen with a heavy element like stannous oxide, yet no disease results (Robertson *et al.*, 1961). This might be predicted from the complete failure to show that stannous oxide has any action whatsoever on biological tissues. Nor does there seem to be any evidence that the presence of so much inert material in the lymphatics and macrophages of the lung will adversely affect its response to infection or other added burdens.

Asbestos, on the other hand, not only produces a severe pneumoconiosis but is believed to be responsible for a high incidence of two distinct malignant lesions—bronchial carcinoma (Doll, 1955) and pleural endothelioma (Wagner *et al.*, 1960). This dust seems to be one that urgently requires further experimental study. Although carcinoma of the bronchus is in the forefront of the clinical problems of this age, the condition is not readily reproducible in animals. Radioactive pellets implanted in the bronchus will produce typical squamous epitheliomata in rats (Nelson, 1961), and a single example of this lesion from diazomethane has been recorded (Schoental, 1960). No explanation can yet be offered for the effects on the lungs of the prolonged exposure to cigarette tobacco smoke.

Delayed Effects

Where a substance enters the general circulation through the lungs, skin, or alimentary tract the likelihood of a prolonged administration producing delayed effects will depend upon a great many different factors. A very important one will be whether the excretion of the toxic material or the products of its breakdown is maintained. Despite the fact that the majority of poisonous or foreign materials that are ingested will eventually be excreted through the kidney, this rarely seems to be the site where the long-term effects of poisons are manifest. The kidney is extremely sensitive to acute damage by single doses of a common poison like mercury. The precise point of binding of mercury with some elements of the renal tubule has been studied in animals (Surtshin and Yagi, 1958). When mercury salts were fed over long periods the only lesions seen in laboratory animals were in the kidneys (Fitzhugh *et al.*, 1950), yet men exposed to mercury may continue to excrete mercury in large quantities without developing any manifestation of renal failure. Instead, if exposure to mercury is excessive the first signs of poisoning in man are disturbances of function in the nervous system.

It is to be expected that any impairment of the function in the central nervous system would be more readily recognizable in man than the earliest signs of renal damage. However, mercury-poisoning does provide an example of a common poison about which it is possible that more might be learnt from experimental toxicology if methods of studying the function of the nervous system were better developed. That kidney injury does not appear commonly as an effect

of a prolonged exposure to poisonous substances may partly explain the comparative lack of interest shown by experimental toxicologists in this important organ.

Before many chemicals—particularly the less water-soluble organic molecules—can be excreted by the kidney they must be rendered water-soluble ; otherwise they pass through the glomerulus and are promptly reabsorbed by the tubules. This step of making a substance more water-soluble is probably one of the most important reactions, if not the most important one, the body shows to the introduction of a foreign chemical. This concept owes much to the work of Brodie *et al.* (1958) in the United States. The cellular components responsible for these metabolic transformations can be isolated, and their behaviour has been studied in the test-tube. Work has hitherto been largely devoted to an elucidation of the various chemical changes, such as oxidation, deamination, dealkylation, or hydroxylation, which compounds of different chemical structure may undergo, and to the enzymes and co-factors that bring about these changes. Recently attention has begun to be paid to conditions which may disturb these important activities. Thus cell fractions isolated from the liver of a rat that has fasted less than 24 hours may be quite unable to perform a reaction readily accomplished by the same fractions from a fed rat (Roth and Bukovsky, 1961). Cell fractions from the liver of a jaundiced rabbit also perform very poorly compared with those from a healthy animal (McLuen and Fouts, 1961). A study of these activities and their significance in the reaction of the intact animal to poisons is, however, only yet at an early stage.

Molecules can also be made more water-soluble by conjugation. A well-known step of this type is a reaction with glucuronic acid, brought about by the enzyme uridine diphosphate glucuronic acid transferase. This enzyme has been intensively studied, for it is in constant operation conjugating bilirubin and sex hormones. Chemicals that the body cannot use, some of which may even be toxic, are continually being absorbed as minor constituents of natural foodstuffs or as the products of bacterial action in the gut. The materials for conjugation, such as glucuronic acid and glycine, are freely available. Drugs, industrial chemicals, or non-nutritive substances added to food will be dealt with by these enzyme systems provided that the foreign chemicals are not so toxic that they injure the liver cells and interfere with these detoxication processes. Thus for a non-toxic material such as benzoic acid that is conjugated and completely excreted there would seem to be no reason why this process should not continue indefinitely. The ingestion of such material over long periods would not therefore be expected to have any untoward effect.

Conjugation and Excretion

For many of the simpler aromatic hydrocarbons which are used widely in industry, conjugation and excretion are remarkably efficient. With the exception of benzene these hydrocarbons have not proved dangerous except in very high concentrations ; then they exert acute effects, usually on the central nervous system. The usual detoxication process is one of side-chain oxidation, followed by conjugation and then excretion. Benzene, having no side-chain, undergoes a complex series of oxidative reactions which, for at least some of it, includes breaking of the ring (Williams, 1959). Benzene, but none of its closely related homologues, has a profound toxic action on the bone-marrow of man, and this can also be demonstrated in various laboratory animals. Gerarde (1960) believes that it may be the products of the oxidation of benzene that are responsible for this action, though he stresses that there is no positive evidence for this. Its power to damage the bone-marrow is a good reason for treating benzene as a very poisonous material, and it is not surprising that as observations on factory workers exposed to benzene have improved in scope and duration the M.A.C. has been progressively lowered.

Apart from the case of benzene, myelotoxic injury seems to be a problem more often met with in therapeutics than as a sequel to exposure to industrial chemicals. It is never possible to be certain that a chemical will not affect some people in this way just because myelotoxic effects were not produced in laboratory animals. Recent work on the haemolytic action of a number of chemicals has shown that certain individuals are unduly sensitive because their red blood cells lack an enzyme glucose-6-phosphate dehydrogenase (Carson *et al.*, 1956). This enzyme is required to maintain adequate levels of reduced glutathione in the red cell (Beutler, 1957). Lowering the level of glutathione makes the red cell, particularly the older cells, more sensitive to haemolysis and it also predisposes to the formation of the blue inclusion bodies called Heinz bodies (Beutler *et al.*, 1955). These red-cell inclusions have been observed among industrial workers exposed to many different aromatic compounds.

The list given in the review by Buckell and Richardson (1950) may be compared with a recent list of chemicals, including some natural products, that produce haemolytic anaemia in sensitive subjects (Larizza *et al.*, 1960). This inborn defect is more common in certain races and may possibly have accounted for the undue sensitivity of four negro children to naphthalene reported some years ago (Zuelzer and Apt, 1949). When the chemical industry spreads to Africa, medical officers may find problems not yet encountered in Europe and North America. This illustration of the role which genetic make-up may play in determining the sensitivity of individuals to chemicals might suggest that a similar type of defect could be related to the sporadic incidence of agranulocytosis among those receiving certain drugs. It also provides an argument against the use of pure-line animal strains in any laboratory screening tests for the toxicity of new materials.

Returning to the metabolism of foreign compounds, it may happen that in making fat-soluble molecules more water-soluble the liver produces a more toxic metabolite. One example from among well-known industrial poisons is the case of tetraethyl lead. This substance is biochemically inert but also insoluble in water, so that if it is accidentally inhaled it must be made water-soluble before it can be excreted. Tetraethyl lead does not concentrate in the brain as is sometimes supposed but is metabolized in the liver, where one of the ethyl groups is removed to form the water-soluble triethyl lead ion (Cremer, 1959). This gets into the circulation, and by its interference with cellular metabolism in the brain it produces a serious and often fatal poisoning. Anyone who began by studying tetraethyl lead in isolated biochemical systems would deduce that it was inert ; however, triethyl lead salts are very toxic. Attempts to understand the mode of action of toxic substances must include *in vivo* and *in vitro* studies in order that a complete picture may be obtained.

Trichloroethylene

The metabolic transformation undergone by a chemical may be very complex and have a bearing in a number of ways on assessing its safety. Trichloroethylene is a very common industrial solvent which has also been used as an anaesthetic. It is generally accepted as being a substance of low acute toxicity, but its widespread use has aroused much interest in its possible long-term effects on man. As a result of numerous studies on animals and on man it is generally agreed that trichloroethylene undergoes a series of metabolic changes soon after it is absorbed. It is probably converted first to chloral hydrate, and this is then oxidized partly to trichloroacetic acid and partly to trichloroethanol. The latter is pharmacologically active, but it is conjugated and rapidly excreted as the glucuronide (Butler, 1949). The M.A.C. for trichloroethylene in various countries ranges from 200 p.p.m. to 9 p.p.m. Swiss and Swedish workers have made extensive studies in factories where trichloroethylene has been used as a degreasing agent (Grandjean *et al.*, 1955; Andersson, 1957). The concentration of trichloroethylene in the factory atmospheres has been compared with the 24-hour excretion of trichloroacetic acid in the urine of the exposed workers. (Ahlmark and Forsmann, 1951; Grandjean *et al.*, 1955).

The important feature of both the Swiss and the Swedish reports is the emphasis placed upon the incidence of subjective symptoms in the workers exposed to trichloroethylene. Although the workers studied in Switzerland were described as being of a very poor general standard, far below that of the average Swiss artisan, the investigators apparently found it possible to give weight to conditions described as "emotional lability," "listlessness," "fatigue," and other similar complaints. The Swedish observers claimed that there was an unusually high incidence of subjective complaints, which included a reduced tolerance to alcohol in people excreting 40 mg. or more of trichloroacetic acid per litre. It is on the basis of an alleged safe level of trichloroacetic acid excretion (20 mg./l.) that the Russian M.A.C. of 9 p.p.m. appears to have been set (Grandjean *et al.*, 1955). The low Russian M.A.C.s for many common industrial chemicals are apparently derived from studies of the effects of these compounds upon "higher nervous activity."

Effects on the C.N.S.

All toxicity-testing procedures on laboratory animals include an examination of the effects of the compounds upon conditioned reflexes, which are rather widely defined. Only atmospheric levels of a vapour that are below those which can produce changes in the behaviour of laboratory animals are regarded as safe for man. While it is not difficult to understand how a substance like trichloroethylene, or carbon disulphide, could have effects upon the central nervous system which are first detectable only by sensitive behaviour studies, it is hard to understand why sulphur dioxide, which is very unlikely ever to reach the brain when inhaled in low concentrations, can have such an effect. It seems possible that some of the modifications in the behaviour of these test animals may not necessarily reflect an adverse reaction but indicate merely that the animal can still smell the substance.

This whole subject has not yet been adequately explored either in the experimental laboratory or in the industrial medical officer's clinic. Probably no one is in a position to say what importance the long-term ingestion of materials at levels liable to affect higher nervous activity will have in relation to occupational disease, either organic or subjective. As standards of industrial hygiene advance it is to be expected that more emphasis will be given to complaints of sleeplessness, fatigue, or irritability as possible reflections of some toxic effects.

While it is obviously difficult to try to decide what will be a safe dose of a substance where the earliest detectable effects are subjective changes such as those affecting behaviour, the position may not necessarily be any easier in the case of the more specific biochemical reactions to toxic substances. Blood or urine levels of toxic materials have been accepted in some but by no means all instances as criteria upon which to base decisions on the safety or otherwise of the degree to which exposure appears to be taking place. It seems probable that measurements of more specific biochemical changes will in the future be more frequently included as measures of exposure.

Already blood cholinesterase levels provide a valuable guide in detecting exposure to the widely used organophosphorus insecticides. Man is richly endowed with this enzyme in his blood-stream; indeed, it is not yet known why he has so much, since he can apparently manage perfectly well if the activity of this enzyme is slowly reduced to 1/10 of that which Nature gave him. If this normal level is depleted, say, by 20%, as might happen over fairly long periods among those spraying insecticides in public-health programmes, should this be considered to be harmful? There is no evidence that laboratory animals suffer in any way from a lifelong partial depletion of their blood cholinesterase. However, if their brain enzyme is depleted by 50% or more, which occurs only after an even more severe depression of the blood enzymes, it is possible to detect slight aberrations in the behaviour of trained rats (Russell *et al.*, 1961). In the present state of ignorance it is probably justifiable to say that any prolonged inhibition of blood cholinesterase in man is undesirable despite a lack of evidence that it is injurious.

A somewhat different attitude seems to be taken with respect to carbon monoxide—a very common hazard both in industry and in ordinary life. There has long been a controversy on whether such a condition as chronic carbon monoxide poisoning really exists. One monograph which stakes a claim for the existence of the condition lists disorders of practically every system as part of the syndrome (Grut, 1949). Judged by modern textbooks on industrial disease and a recent detailed study (Lindgren, 1961), the consensus of opinion is that there is no such condition as chronic carbon monoxide poisoning. Now, carbon monoxide reacts with another element present in relative abundance in our blood, and it seems to be generally accepted that the presence of 5% COHb in the blood is of no consequence. Nevertheless it was possible to demonstrate a slight effect on the visual acuity of healthy young men by inducing this degree of carbon monoxide saturation of haemoglobin (Macfarland *et al.*, 1944). No one has yet established a link between persistent degrees of carbon monoxide saturation of the blood and human disease. Perhaps this provides support for the idea that the human body can tolerate a certain minor degree of injury for long periods without serious consequences suddenly making their appearance. The situation with regard to carbon

monoxide also illustrates the point that well-known poisons seem to excite less anxiety than new chemicals, whether poisonous or not.

Poisoning after prolonged exposure to a toxic material may result from the fact that the substance has accumulated or remained for long periods in the body. Arsenic in small quantities may collect in the hair and nails and do little damage, but lead collects in the bones and the first toxic effects are seen as disorders of haemoglobin metabolism in the adjoining bone-marrow. The effects of radium on bone are also well known.

Another tissue in which accumulation can take place is fat. The importance of fat as a reservoir for surplus material circulating in the blood is only now coming to be recognized. The short-acting barbiturates owe their effects to the fact that after an intravenous injection the blood level rapidly falls below an anaesthetic level as the compound disappears into the fat (Brodie *et al.*, 1950). As the blood level falls as a result of metabolism of the barbiturate in the liver the surplus is then slowly released from the fat into the blood, but in sub-anaesthetic levels. The same course of events probably occurs in trichloroethylene anaesthesia. In the case of carbon tetrachloride it has been shown that by far the greatest fraction of a single dose goes into the fat (McCollister *et al.*, 1951). It seems very probable that the hangover from acute poisoning by many highly fat-soluble materials may be due to this, and any so-called safe level of exposure to such materials should only be to doses that will not lead to a progressive accumulation of the compound in fat.

The fat itself seems to serve as a passive receptacle. Thus D.D.T. is readily laid down in the fat of rats which receive D.D.T. in their diet (Laug *et al.*, 1950). The same is true if D.D.T. is given to man (Hayes *et al.*, 1956). The animals show no untoward effect unless they are partly fasted. The D.D.T. is then released and produces its characteristic poisonous effects on the nervous system. However, extensive biochemical tests have shown that the fat tissue itself is not adversely affected even by concentrations of D.D.T. which would impair the metabolism of liver-cell constituents (Parker, 1960). If for any reason a material that had been laid down in fat was rapidly released it might produce its characteristic acute or subacute effects. Despite the obvious undesirability of allowing it to happen we cannot conclude, on such evidence as exists, that the prolonged ingestion of a material that will be laid down in fat would for this reason produce any novel toxic effect. However, no one could pretend that the evidence for this, reassuring though it may be, is anything but fragmentary.

Chemical Carcinogens

Of all the hazards that may arise from the ingestion of chemicals anywhere in our environment none creates more apprehension than the possibility that cancer may result. Work on the mechanism of carcinogenesis has received much stimulus from the study of chemical carcinogens which were themselves first recognized because of an unusual incidence of certain cancers among those in particular occupations. The skin, the respiratory tract, and the urinary tract, but hitherto neither the liver nor the alimentary tract, have been recognized as sites for chemically induced cancers in man. The liver, however, is one of the commonest sites of experimental tumours produced by chemicals in laboratory animals. It is indeed a very common natural disease in certain parts of the world, but these do not include industrial areas. The possibility that these liver tumours in man are produced by chemical carcinogens, perhaps of plant origin, has by no means been excluded. It is often assumed that the tumours which develop in workers exposed to carcinogenic substances arise because they have ingested or absorbed small quantities of these substances over a very long time. Recent experimental work and current views of the origin of cancer make it worth re-examining this proposition. The relation of tissue injury by chemicals and the development of cancer has been reviewed by Magee (1961), on the basis of his work on liver and kidney tumours produced by a solvent that was once considered for industrial use—dimethyl-nitrosamine.

The theory that chronic irritation was an essential precursor of cancer, put forward with the authority of Virchow, has now largely been abandoned. That cancer develops as a two-stage process in which the chemical initiator brings about changes in or around the cells that ultimately become malignant, while the transformation itself is due to other factors, may well be true in man as it appears to be in certain experimental procedures used on animals. Indeed, "chronic irritation" might under some circumstances provide the second-stage stimulus, but it is the initial stages which must be considered in relation to the possible effects of prolonged exposure to small quantities of a carcinogen.

The somatic mutation theory implies some change brought about in the cell which is transmitted to the daughter cells. Such changes may occur in the nucleus, but it is now thought by some that visible chromosomal changes are the result rather than the cause of malignant cell growth. Chemical changes in the deoxyribonucleic acid (D.N.A.) of the nucleus can be readily brought about in the test-tube—for example, by alkylating agents—and have been shown to take place in the mouse (Brookes and Lawley, 1960) and the rat (Farber and Magee, 1960). The alkylated guanine which is present in the D.N.A. has been shown to produce chemical instability of the polymers, and it is possible that such faulty D.N.A. could lead to a cell having incomplete control of its metabolism.

The possible importance of the cell cytoplasm as a place in which carcinogenic changes may be initiated has come to the fore as a result of recent work on viruses. Cytoplasmic ribonucleic acid (R.N.A.) is also methylated by dimethylnitrosamine, and on current hypotheses such changes might initiate the development of a particle with some of the properties of a cancer-producing virus, or lead to faulty protein synthesis within the cell. This in turn could bring about enzyme deletion or immunological modifications, both of which occupy prominent places in current theories of the origin of cancer. The important common factor here is the demonstration that alkylating agents can change the composition of D.N.A. and R.N.A., and some of these alkylating agents are carcinogens. With diazomethane and N-nitroso-methyl urethane Dr. Schoental has produced tumours of the bronchus, oesophagus, stomach, and subcutaneous tissues, sometimes with single doses. Malignant tumours of the kidney will develop in rats several months or more after a single dose of dimethylnitrosamine of a size that produces a severe but reversible liver lesion but no immediate injury to the kidney (Magee and Barnes, 1959).

Another well-known carcinogen which can produce tumours in mice after single doses is urethane; the biochemical mechanisms have been discussed by Rogers (1961). On the mutation theories of cancer it has been thought that a long-term exposure to small quantities of a carcinogen would be dangerous in so far as this would increase the chances of a molecule of the carcinogenic chemical making contact with the "sensitive" constituent of the cell and so initiating the irreversible change. However, this recent work with carcinogens which are effective in single doses makes it seem at least as probable that the laws of mass action will apply in this as in other chemical reactions. Perhaps the immunological principle of optimal proportions might also determine the most effective reaction between a carcinogen and cell constituents, so as to lead to the development of a tumour. While dimethylnitrosamine will produce 100% of liver cancer at one dose level within 40 weeks, at a tenth of that dose it produced no pathological change at all in the course of 104 weeks of administration (Magee and Barnes, 1956). Thus there certainly is a safe dose of some carcinogens. However, the main point to be emphasized is the need to reconsider the way in which an exposure to a chemical carcinogen can be dangerous.

A single accident in which gross over-exposure occurs may in some cases be more dangerous than a lifetime's exposure to much smaller quantities. Clearly, under practical conditions where there was repeated exposure to a compound in small quantities more often than not the chances of gross over-exposure taking place on isolated occasions would be increased. However, if this did not happen there seems no reason to fear particularly an exposure to small quantities just because this did continue for a very long time. However, it is unlikely that all chemical carcinogens behave alike, and there is an urgent need for a great deal more experimental work in order to understand more clearly the relation of dose, duration of exposure, and other factors involved in the initiation of malignant changes in tissues by specific chemicals.

Conclusions

Intermittent or more continuous exposure to chemicals with a tremendous variety of biological properties is undergone by many people during their work in industry, their life in our cities, and even in the privacy of their homes. In some polluted atmospheres the quantities of toxic materials seem to border on those demonstrably hazardous. In others—for example, the field of food additives—most of the materials appear by current standards to be virtually harmless. In other situations, particularly where occupational exposure is concerned, the chemicals may produce some deviation from normal the significance and importance of which are at present not fully understood.

Unfortunately, there are only very limited resources available either in this country or overseas for the experimental study and proper analysis of the properties and mode of action of toxic substances. In recent years the balance of this effort has been grossly disturbed by the current clamour about the safety of chemicals used as food additives (Mulford, 1961). Increasingly greater laboratory facilities are being devoted to the carrying out of set procedures to show that substances almost biologically inert can be tolerated by rats and dogs for years on end. There are, however, still quite a number of really poisonous materials, particularly in the environment of those in certain occupations. It is surely important to see that, in this country at least, more attention will be paid to the problems presented by such materials.

No one doubts the potential importance of irritant gases and particles in producing disease of the respiratory tract, yet are there in this country enough modern well-equipped laboratories for studying these experimentally? Few doubt the importance of cerebral activity and human behaviour, and nearly everyone is aware how easily this may be disturbed by simple things like fatigue or ill-chosen food. Many toxic chemicals have their most important effects upon the central nervous system, and some examples given above illustrate the limitations of animal experiments in detecting these, though their importance has been shown by observations on man.

Without any need to embrace the Pavlovian dogma so dear to the biologists of Eastern European countries, there seems very good reason for making a much more adequate study of the effects of certain toxic chemicals on animal behaviour as one means of detecting toxic effects at an early and, one hopes, at a reversible stage. No one will dispute the probability that a better understanding of the hazards presented by toxic chemicals in industrial or other environments will come from a more comprehensive examination of their mode of action in experimental animals. However, these findings must continually be related wherever possible to clinical observations on exposed people.

As our standards rise it is natural that the biochemist's bench or even the psychiatrist's couch will come to be regarded as being more satisfactory than the pathologist's slab as places from which to draw conclusions about the dangerous property of a chemical to which man is newly exposed. However, as the diagnostic criteria become more and more sensitive so does the problem arise of being able to say when a certain deviation from normal is something that should or should not be tolerated under the practical conditions in a modern civilization.

The need for common sense to prevail applies in this field as in any other involving human activity. At present one of the greatest needs for common sense seems to be to ensure that scientific research in the field of toxicology is applied to the situations where real hazards are known to exist.

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"I have said that we should try to think with the whole of our past. One of the thoughts most strongly induced by this practice concerns the unevenness of progress. The most striking gains prove, on examination, to have involved serious loss. An example is alphabetic writing. This surely, one would think, is a wholly beneficent achievement of human ingenuity. It was, in fact, a necessary pre-condition of the emergence of large-scale organization, yet it wrought so decisive a change in human consciousness that it all but obliterated the memory, and certainly destroyed the understanding, of the age-old culture of pre-literate societies. The invention of the alphabet blinded men to the knowledge of some thousands of years of our human story. Much research and a great effort of the historical imagination were needed to restore to the twentieth century an appreciation of the oral cultures which writing destroyed. Yet so accomplished a stylist as Plato was near enough to the world of oral tradition to view the dissemination of the alphabet with a critical eye. He had two main fears. One, that writing would impair the memory. Has it not done so? 'Without writing,' notes Tom Harrisson, 'memory is perfect, tradition exact.' Secondly, Plato felt that a book was an inadequate substitute for a living teacher. We may note that the two greatest teachers in the European tradition, Socrates and Jesus, never wrote a book. In our own educational practice at its best, books are treated only as an adjunct to the spoken word." ("Science and the Classics," Professor B. Farrington, *Nature*, September 30, 1961.)

TOBACCO SMOKING AND VENTILATORY FUNCTION OF THE LUNGS

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It is a matter of everyday clinical observation that the majority of patients with chronic obstructive lung disease* give a significant history of tobacco smoking. In the minds of many this leads to the undocumented extrapolation that "smoking causes bronchitis."

A number of clinical studies have convincingly demonstrated an increased incidence of cough and sputum among smokers (see Higgins, 1959). Studies relating objective assessment of lung function to smoking habits are less susceptible to simple or uniform interpretation. At the international level (United Kingdom *versus* Denmark) a higher incidence of smoking in a community (U.K.) has been shown to be associated with a lower mean maximum breathing capacity (M.B.C.) (Olsen and Gilson, 1960). Smokers have been found to have a lower mean M.B.C. than non-smokers in both urban and rural areas of Great Britain (Higgins, 1957, 1959). Maximal expiratory flow rate (M.E.F.) has been shown to diminish more rapidly with increasing age in smokers than in non-smokers in a group of hospital in-patients (Flick and Paton, 1959). On the other hand, the diminution in ventilatory capacity does not run parallel with the amount of tobacco smoked (Higgins, 1959); differences between cigarette smokers and pipe smokers are sometimes more marked than differences between cigarette smokers and non-smokers (Olsen and Gilson, 1960); the scatter of ventilatory capacity among smokers as a whole is wide (Flick and Paton, 1959); and the position of ex-smokers is obscure (or even ignored) in some studies.

Sydney has a mild climate and an atmosphere that is relatively unpolluted compared with many parts of Northern Europe. Clinically, gross bacterial infection of the airways is far less common in patients with chronic bronchitis in Australia than it is in Great Britain. It was felt that a pilot study of ventilatory function in relation to smoking habits under these conditions might yield more straightforward data than earlier studies.

Methods

The subjects of the study were 302 people, aged 18 years or more, interviewed in the out-patient department of Sydney Hospital, in the following groups: (1) ambulant out-patients waiting to be seen at the gynaecology, urology, neurosurgery, general surgery, and dermatology clinics (general and special medical clinics were specifically avoided); (2) friends waiting with patients; (3) members of the medical, nursing, and lay staff associated with these clinics. On certain mornings and

*This term, recommended by a Ciba Guest Symposium (1959), is used in preference to the terms "chronic bronchitis" or "emphysema."

afternoons a female clerk unselectively asked people in these categories to co-operate in a simple investigation. Refusals were rare. From among these subjects only those with a personal history of bronchial asthma were subsequently excluded before analysis of the results.

For each subject a form was completed, giving details of age, height, weight, and occupation; and a personal history of respiratory illness and current respiratory symptoms (cough, sputum, dyspnoea). A detailed smoking history was obtained after this in an effort to avoid observer bias. All forms were completed by the same medical observer.

Each subject then performed a series of five maximal forced expirations into a Wright peak flow meter (Wright and McKerrow, 1959). The best value of the five was used in the presented results. All determinations of maximal expiratory flow rate were supervised by one observer.

A non-smoker was regarded as a person who had never smoked more than one cigarette a day for one year. All ex-smokers had ceased smoking at least three months earlier, so that no difficulty arose in separating smokers from ex-smokers.

Results

Table I shows the distribution of the 302 subjects by sex and smoking history. From the results obtained for maximal expiratory flow rate (M.E.F.) in non-smokers with no cough or sputum (44 males, 76 females) the best predicting regression equations were calculated for the prediction of "normal" M.E.F. in each sex at various ages (Selby and Read, 1961). These regression equations were:

TABLE I.—*Distribution of Subjects by Sex and Smoking Habits*

	Males	Females
Non-smokers	46 (27%)	81 (61·5%)
Smokers	91 (53·5%)	43 (32·5%)
Ex-smokers	33 (19·5%)	8 (6%)
Total	170	132

$$\text{M.E.F. (l./min.)} = 3.2\,H - 2.1\,A + 71 \quad \text{(males)}.$$

$$\text{M.E.F. (l./min.)} = 452 - 1.2\,A \quad \text{(females less than 60)}.$$

(H = height in cm.; A = age in years.)

With these regressions a "normal expected" M.E.F. could be calculated for each subject in the entire series, and each observed M.E.F. could then be expressed as a *plus* or *minus* difference from the predicted value. The effects of body stature and the normal ageing process were thus standardized for the whole group. The individual results have been expressed in this fashion in Figs. 1 to 4, in which variation of observed from predicted M.E.F. is plotted against age. By definition on such a grid, the non-smokers without symptoms will have a mean on the zero line and a "range" extending 2 standard deviations above and below it. This mean and range are represented in Figs. 1 to 4 by the dotted lines. Any additional effects attributable to smoking should emerge as further downward regressions.

The results in the two non-smoking males with cough and sputum fell below the normal range.

Fig. 1 shows the results for male smokers who denied having any cough or sputum. Most fell within the normal range, but, looked at as a linear regression group, they did differ from non-smokers. They lost, on the average, an additional 2.23 litres per minute of M.E.F. each year compared with asymptomatic non-smokers, and the difference in regression is significant ($P<0.01$). In the individual cases the amount smoked did not appear important in determining the degree of ventilatory incapacity.

Male smokers with cough only (Fig. 2) formed a small but compact group. They lost an average of 3.2 litres per minute of M.E.F. each year more than asymptomatic non-smokers. They differed significantly from non-smokers ($P<0.01$), but the difference between them and smokers without symptoms did not reach conventional levels of significance. Again, the amount smoked in the individual case did not appear crucial.

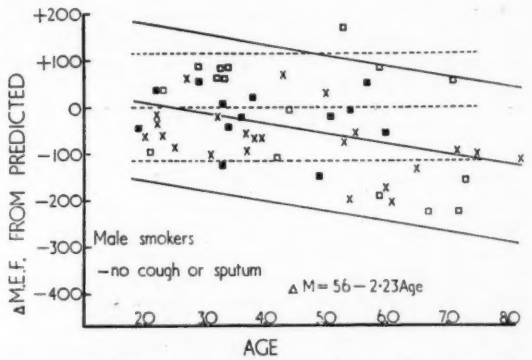

FIG. 1.—Ventilatory studies in asymptomatic male smokers (52). Ordinate: Variation of observed M.E.F. from predicted in litres per minute (see Results). Abscissa: age in years. The dotted lines represent the mean and ±2 standard deviation range for asymptomatic non-smokers. Black squares: Heavy smokers; white squares: light smokers; crosses: moderate smokers.

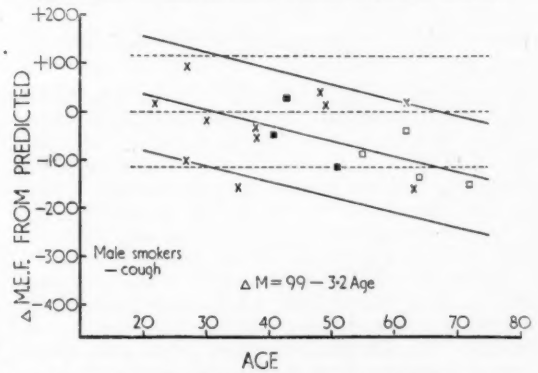

FIG. 2.—Ventilatory studies in male smokers with cough only (18). Conventions as in Fig. 1.

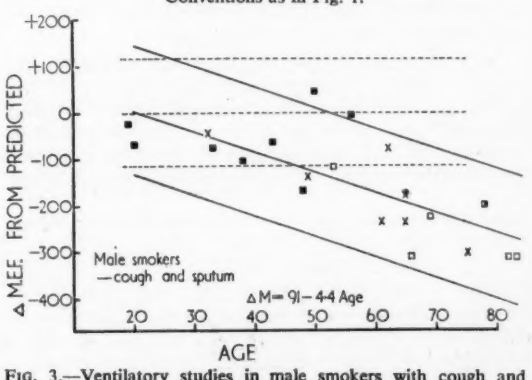

FIG. 3.—Ventilatory studies in male smokers with cough and sputum (21). Conventions as in Fig. 1.

Male smokers with cough and sputum (Fig. 3) showed an even greater loss of ventilatory function with increasing age. They lost, on the average, 4.4 litres per minute of M.E.F. each year more than asymptomatic non-smokers. The difference from non-smokers was highly significant ($P<0.001$) and that from smokers without symptoms just so ($P=0.05$). The "mean" line for this group fell below the lower limits for asymptomatic non-smokers from the late forties onwards.

Ex-smokers (Fig. 4) formed a good replica of the asymptomatic non-smoking group. They had ceased smoking from 3 months to 40 years earlier. Even those with cough and sputum (black dots, Fig. 4) did not in general show the marked loss of ventilatory capacity seen in smokers with those symptoms. Only 2 out of 33 ex-smokers, both with cough and sputum, fell appreciably below the non-smokers' range.

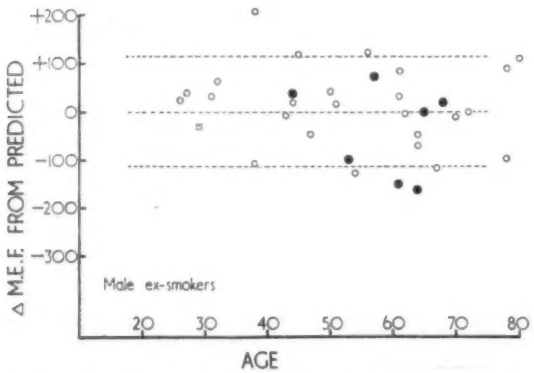

FIG. 4.—Ventilatory studies in male ex-smokers (33). Black dots represent those with cough and sputum.

The results among women did no more than show a similar trend to the results among men: on statistical grounds they were not nearly so clear-cut. This may have been partly due to the smaller numbers of female smokers in each symptom-group, and especially of those over the age of 55. To summarize the female data: three (out of five) non-smoking women with symptoms had M.E.F.s within but at the lower limit of the asymptomatic non-smokers' range. Female smokers with no symptoms or with cough only did not differ significantly in ventilatory capacity from non-smoking females. Female smokers with cough and sputum showed a falling off of ventilatory capacity similar to that seen among males with these symptoms, but the correlation did not reach conventional levels of significance.

Table II shows the overall incidence of cough and sputum among smokers and non-smokers. The influence of duration of smoking and amount smoked (averaged over smoking life) on the incidence of symptoms (cough, or cough *plus* sputum) was examined for the male subjects. There was no significant increase in the incidence of symptoms in increasing ten-year age-groups ($\chi^2=8.405$; $n=5$; $P=0.1$–0.2), nor did the incidence of symptoms differ significantly as between light (1–14 g./day), moderate (15–24 g./day), and heavy (>25 g./day) smokers ($\chi^2=0.764$; $n=2$; $P=0.5$–0.7).

TABLE II.—*Percentage Incidence of Symptoms in Various Groups*

	Males		Females	
	Cough + Sputum	Cough ± Sputum	Cough + Sputum	Cough ± Sputum
Non-smokers	4·4	4·4	4·9	6·2
Smokers	23·1	42·9	18·6	48·8
Ex-smokers	21·2	30·3	—	—
Smokers/non-smokers ratio	5·3	9·8	3·8	7·9

The group contained no pure cigar smokers, and only five pure pipe smokers. All five had M.E.F.s closer to the mean for cigarette smokers of the appropriate age and symptoms than to the mean for non-smokers.

Discussion

Note must be taken of the nature of the population used in the present study. It was certainly not a random population sample such as those of Higgins (1957, 1959) or Olsen and Gilson (1960). On the other hand, the use of ambulant "non-medical" out-patients, their friends and attendants, should obviate many of the objections to the use of hospital populations in general. The present group should be more representative of the general population than the hospital in-patient group studied by Flick and Paton (1959). Among the non-smoking asymptomatic subjects the results were examined separately for "patients" and "friends and staff." At all ages the mean values for M.E.F. were almost identical in the two groups.

The determination of M.E.F. with the Wright peak flow meter appears to be an acceptable measure of ventilatory function at the epidemiological level. Higgins (1957) found a high degree of correlation between the M.E.F. so measured and the M.B.C. Supervision of all the ventilatory tests by one observer should have overcome the variation in M.E.F. sometimes obtained by different observers in the same subjects (Dr. C. M. Fletcher, personal communication).

In seeking information about respiratory symptoms the subjects were first asked whether they ever coughed, and if so when and how often. If they denied cough, the question was reiterated as, "So you never cough, not even first thing in the morning?" A similar routine was followed in obtaining information about the sputum. Those who coughed at all first thing in the morning or who brought up any sputum at all were counted as having cough or sputum respectively. This did not provide the same detailed information of the admirable M.R.C. (1960) questionary on respiratory symptoms. However, Elmes *et al.* (1959) found that a person's replies to questions about cough and sputum do not necessarily correspond closely with the data recorded for him under observation, and we sought some basis for division, albeit relatively coarse, into groups with different clinical responses of the bronchial mucosa to the environment. In terms of likely errors, the group who denied cough and sputum is probably the most heterogeneous, containing some subjects with one or both symptoms. The group with "cough only" might really contain some with minimal amounts of sputum. The group who admitted both cough and sputum is unlikely to contain subjects with neither symptom.

Even granting the coarseness of the clinical criteria, separation into groups based on them led to certain functional correlations among male subjects. Among non-smokers the few with cough and sputum had a lower M.E.F. than those without these symptoms. Asymptomatic smokers showed a reduction of mean M.E.F. compared with asymptomatic non-smokers, but the presence of either cough or cough with sputum was associated with further decrements in ventilatory

function. There was no distinction on the basis of M.E.F. between those who coughed only first thing in the morning and those who coughed during the day. To reduce the regressions to some absolute values, an average man aged 60, and 175 cm. tall, was likely to have an M.E.F. of 505 litres per minute if he was an asymptomatic non-smoker, compared with 322 litres per minute if he was a smoker with cough and sputum.

Elmes *et al.* (1959) demonstrated an inverse relationship between sputum volume and indirect M.B.C. in 118 London postal workers without regard to smoking habits. The present data confirm and extend the significance of their findings in showing a gradient of ventilatory loss from non-smokers, through smokers without symptoms, those with cough alone, and those with cough and sputum.

Division of smokers into three groups by symptoms illustrates a further point. Flick and Paton (1959) found a very wide range of values for ventilatory capacity among smokers in general with increasing age. In the present series separation of the smokers by symptoms has provided three groups of subjects with individual ranges of ventilatory capacity very little wider than that for asymptomatic non-smokers. In other words, Flick and Paton's "variable effect of smoking in different persons" at the ventilatory level is reflected in their symptomatic responses to smoking. At the international level, it is of interest that the rate of fall of M.E.F. in males with age in Higgins's (1957) general population sample in South Wales (6.34 litres per minute each year) is comparable with the rate of fall in the worst-affected group in the present series, smokers with cough and sputum (6.5 litres per minute each year, made up of 2.1 litres per minute for males in general and 4.4 litres per minute for their specific group). This would support the belief that chronic bronchitis and its sequelae are less dramatic in progression in Australia than in the United Kingdom; and add to the validity of the present study as one in which the effects of smoking are less complicated by "background" influences.

The data for ex-smokers (Fig. 4) indicate that the loss of ventilatory function associated with smoking need not necessarily be permanent. In general, M.E.F. in this group is entirely comparable with that for lifelong non-smokers. Even when cough and sputum persist (black dots, Fig. 4) most subjects' ventilatory function falls clearly within the normal range instead of showing the striking reductions of Fig. 3. Other considerations apart, these results suggest that, under atmospheric and climatic conditions such as those in Sydney, patients with reduced ventilatory capacity (with or without cough and sputum) may be advised to give up smoking with some confidence that their ventilatory function will improve. Only two ex-smokers with cough and sputum remained below the normal range for M.E.F.—essentially the same incidence (6%) as among non-smokers (4.4%).

Table II shows the incidence of these apparently important symptoms among smokers and non-smokers. Smoking is associated with a fourfold to fivefold increase in the incidence of cough plus sputum and an eightfold to tenfold increase in the incidence of all bronchitic symptoms.

It could be suggested that this increased incidence of bronchitic symptoms among smokers merely reflects a simple quantitative effect of tobacco smoking on the bronchial mucosa. If this were so, two corollaries ought to follow: increased tobacco consumption and increased duration of smoking should be associated with an increased incidence of symptoms. It was demonstrated that neither of these two corollaries is true of the present data. Higgins (1959), too, "surprisingly" found no trend in M.B.C. with increasing tobacco consumption. (It is only fair to point out that by using another approach in *part* of the whole series a different interpretation might be reached: considering only smokers less than 50 years old, the asymptomatic group contains an excess, and the symptomatic group a deficiency, of light smokers. But, *per contra*, this relationship does not hold for those over 50.) Within individual subgroups of smokers, Figs. 1, 2, and 3 illustrate that there was no tendency for heavy smokers to have poorer ventilatory function than light smokers. Since the smoking categories were based on whole-of-smoking-life averages, they are not likely to be heavily biased by changes of smoking habits late in life consequent upon the development of symptoms or incapacity.

Genetic and Environmental Factors

The data thus do not support the hypothesis that smoking has a simple quantitative effect on the bronchial mucosa. Any alternative hypothesis must be largely speculative, but a study of the present data indicated that, within certain limiting assumptions, they were compatible with a hypothesis linking genetic and environmental factors.

Assume the existence of two alleles V and v such that homozygous VV subjects develop bronchitis and marked ventilatory loss even in the absence of external irritants, homozygous vv subjects do not develop bronchitis or marked ventilatory loss even in the presence of external irritants, and heterozygous Vv subjects only develop bronchitis and marked ventilatory loss in the presence of external irritants. In the present context the external irritant is tobacco smoke, but it might equally include atmospheric pollution and many other factors. The incidence of VV homozygotes in the group may be found from the proportion of non-smokers with bronchitic symptoms. The proportion of asymptomatic subjects among smokers would give the incidence of vv homozygotes.

In the Appendix it is demonstrated that the distribution of subjects by symptoms in the present study is entirely compatible with such a genetic hypothesis. There is one obvious statistical objection to its too ready acceptance: the calculations in the Appendix (though not the thesis itself) assume random genetic distribution among smokers and non-smokers. It has been pointed out that VV homozygotes, because of their "genetic weakness," might tend not to take up smoking or else rapidly to become ex-smokers. Also, heavy smokers appear to differ from light and non-smokers on one genetic ground—ability to taste P.T.C. (Thomas and Cohen, 1960). On the other hand, data which "fit" separately for males and females, and indicate similar allele frequencies for the two sexes, probably add a little further support to our thesis.

Such a hypothesis then would postulate a genetically determined reaction of the bronchial mucosa to an external irritant such as tobacco smoke. There is nothing intrinsically unacceptable in such a postulate on biological grounds. The similar incidence of cough and sputum plus reduced ventilatory capacity among non-smokers (4.4%) and ex-smokers (6%) could be interpreted by suggesting that these were the VV

homozygotes in each group. Among smokers, genotype would determine whether a subject remained asymptomatic and lost a moderate amount of ventilatory capacity, or developed bronchitic symptoms and lost a good deal more. On such an all-or-none basis for symptoms the amount and duration of smoking would cease to be a prime factor as in the present and in Higgins's data. Among ex-smokers the incidence of cough plus sputum was the same as that among smokers, but the incidence of cough alone was much less; it is suggested on this basis that the persistence or otherwise of symptoms in ex-smokers depends on their relative severity.

At present this hypothesis is offered as a speculative but not unsupported alternative to a direct and quantitative deleterious effect of tobacco smoking on the bronchial mucosa. It appears to merit further investigation.

Summary

Ventilatory capacity has been assessed in 302 subjects in Sydney in relation to smoking habits and respiratory symptoms. Among males, smoking, in the absence of symptoms, leads to some reduction of ventilatory capacity. The presence of cough or cough and sputum is associated with further impairment of ventilatory function. These same symptoms are associated with loss of ventilatory capacity among non-smokers. The ventilatory loss appears to be largely reversible in those who cease smoking. Among females there are similar trends, but the results are not nearly so clear-cut.

The data are not apparently explicable on the basis of a simple quantitative effect of smoking on the bronchial mucosa. As alternative hypothesis based on a combination of genetic and environmental factors is offered, and this alternative hypothesis is supported by the present findings.

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APPENDIX

Among males, assuming random genetic distribution among smokers and non-smokers, and using the groupings in "Discussion":

Incidence of ? VV homozygotes=0.044 (2/46)
Incidence of ? vv homozygotes=0.571 (52/91)
Incidence of ? Vv heterozygotes=0.385 (by subtraction)

If these proportions obtained throughout the whole group of smokers and non-smokers (137) we would have 6.0 ? VV subjects, 52.7 ? Vv subjects, and 78.3 ? vv subjects.

On the basis of the Hardy–Weinberg law (Stern, 1949), we may calculate the expected number in each group if they follow the postulated genetic pattern, using the observed incidence in the ? homozygous groups and the ? heterozygous group to calculate allele frequencies. On this basis, the allele frequency of V (p) is 0.236 (VV+½Vv) and of v (q) is 0.764 (vv+½Vv). The expected frequencies of VV (p^2), Vv (2pq), and vv (q^2) subjects are thus 0.056, 0.361, and 0.584 respectively, and the expected numbers among 137 subjects become 7.6 VV, 49.4 Vv, and 80 vv These correspond closely with the observed figures above, and on a statistical basis do not differ significantly from them ($\chi^2=0.5933$; n=2; P=0.7–0.8). As a further indication that the observed incidences would closely fit such a genetic hypothesis, we may apply the criterion that $\sqrt{VV}+\sqrt{vv}$ should equal 1. In this case they equal 0.964, a disagreement of less than 4% *pro rata*.

A similar measure of agreement may be calculated for the female data. The allele frequencies for females become 0.275 for V and 0.725 for v, not very different from the calculated male frequencies.

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TOBACCO SMOKING AND SERUM LIPIDS IN OLD MEN

BY

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The interrelationships between coronary heart disease, serum lipids, and cigarette-smoking have been demonstrated by authors from several countries in recent years (Hammond and Horn, 1954; Gertler and White, 1954; Gofman *et al.*, 1955; Doll and Hill, 1956; Thomas, 1958; Karvonen *et al.*, 1959; Dawber *et al.*, 1959; Bronte-Stewart, 1961). Their work has, however, been chiefly concerned with men below or during middle age, whereas it seems that over the age of 65 years there is little relationship between death from coronary heart disease and a previous history of smoking (Doll and Hill, 1956) or between clinical evidence of myocardial ischaemia and raised serum cholesterol (Oliver, 1958; Acheson, 1961). It is therefore a matter of some interest whether serum lipids are related to smoking habits in men aged 65 and over.

Material and Method

The Sample.—The men were all pensioners on the list of Messrs. Arthur Guinness Son and Company Ltd. (Dublin), and their names were selected in a random manner as follows: every man aged between 75 and 85 was chosen, between the ages of 70 and 74 every third name was omitted from the list, and between the ages of 65 and 69 alternate names were omitted. This method of selection produced 267 names in all, and each man was sent a postcard inviting him to attend in the company's medical department for clinical examination; the actual attendances (221) are shown

by age in Table I, together with the numbers for whom estimations of serum cholesterol and an analysis of the serum proteins by paper electrophoresis were satisfactory.

TABLE I.—*The Sample*

Age in Years	Number of Men						
	Invited to Attend	Attended		With Complete Cholesterol Assessments		With Complete Serum Electrophoresis	
		No.	%	No.	%	No.	%
65–69	92	82	89	74	80	72	78
70–74	100	86	86	83	83	77	77
75–79	40	29	72	29	72	29	72
80–85	35	24	69	23	66	23	66
Total	267	221	82	209	78	201	75

Clinical Examination and Lipid Estimations.—Full details have already been published of clinical procedures (Acheson and Acheson, 1958; Acheson, 1961) and of biochemical and electrophoretic techniques (Acheson *et al.*, 1958; Acheson and Jessop, 1961); accordingly only an outline will be given here. The clinical examination, which was carried out by one of us (R. M. A.), included a history of smoking habits and a note about diet that permitted a rough appraisal of whether or not these old men fed themselves adequately. Blood was taken in a dry syringe between 9 a.m. and 11 a.m., after breakfast, and within 90 minutes the serum was separated by centrifuging. The serum cholesterol was estimated by three independent observers, one of whom used the method of Sackett (1925) and two that of Anderson and Keys (1956); and since the findings by the two methods did not differ systematically the results were averaged, when the three estimations were within 10% of the highest of the three. In the relatively few cases where they were not, assessments were repeated until the required agreement level was reached. Paper electrophoresis, with certain minor modifications, was carried out by the technique of Dangerfield and Smith (1955), using a horizontal EEL apparatus and a barbitone buffer (*p*H 8.6). Each strip was divided in two, light green S.F. (" lissamine " green) being used to stain the serum proteins and sudan black for the lipoproteins. The intensity of staining in the various bands was measured with an automatic reflectance scanner which incorporated its own integrator.

Tobacco and Dietary Indices.—For certain of the calculations tobacco and dietary indices have been used. For the tobacco index 1 oz. (28 g.) of tobacco a week and 5 cigarettes a day were taken as unity. Thus a man who smoked 20 cigarettes a day had an index value of 4, and another who smoked 10 cigarettes a day and 3 oz. (85 g.) of pipe tobacco a week had a value of 2+3=5. The dietary index simply enumerated the number of times a man ate meat, fish, or egg in a week; it ranged from 0 to 19, and, although it is obviously a very rough measure, the serum albumin was significantly higher in those with an index of 14 than in those with an index of less than 2; and men with an index of 2 or under had significantly less subcutaneous adipose tissue than the remainder of the sample (Acheson and Jessop, 1961).

Results

Relationship of Serum Cholesterol and Smoking With Age

The distribution of serum cholesterol in the sample is shown by five-year age-groups in Fig. 1 and that of β/α lipoprotein ratio in Fig. 2. There tended to be absolutely and relatively fewer men with a serum cholesterol in excess of 220 mg. among the older age-groups, with the result that the mean value fell slightly

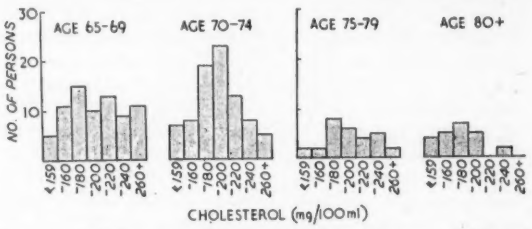

FIG. 1.—Histograms showing distribution of serum cholesterol in sample by five-year age-groups.

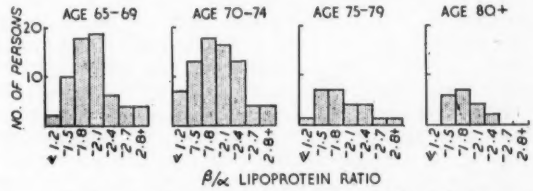

FIG. 2.—Distribution of β/α lipoprotein ratio by five-year age-groups.

but significantly with age ($r=-0.19$; $P<0.01$). The pattern of smoking varied in a far more striking manner with age (see Table II); 66% of the men aged 75 years and over were pipe smokers and 9% cigarette smokers, as compared with 27% pipe smokers and 53% cigarette smokers in those who were less than 75.

TABLE II.—*Smoking Habits by Age Among Men with Cholesterol Assessments*

Type of Tobacco Used	Age in Years					
	Under 75			75 and Over		
	No.		%	No.		%
None	26		17	12		23
Cigarette only	83		53	5		9
<20 day		45	29		2	4
>20 day		38	24		3	5
Pipe only	42		27	35		66
Cigarette and pipe	5		3	1		2
Total	156		100	53		100

Relationship Between Serum Lipids and Smoking

The nature of the relationship between smoking and both serum cholesterol and β/α lipoprotein ratio is indicated in Table III. This shows that both measures of serum lipid are just a little higher in non-smokers or very light smokers than in the heavier smokers of cigarette or pipe tobacco. This trend is confirmed by the correlation analysis shown in Table IV, where it

TABLE III.—*Relationship of Cigarette and Pipe Smoking with Serum Cholesterol and β/α Lipoprotein Ratio*

Type of Tobacco Used	Mean Serum Cholesterol (mg.)		Mean β/α Lipoprotein Ratio	
	No.	Mean	No.	Mean
None	38	214	36	2·0
Cigarette only; No./day:				
5	12	201	11	2·1
10	34	213	33	1·9
20	33	201	33	1·9
30 and over	8	206	8	1·8
Pipe only; oz./week:				
1	3	203	3	2·2
2	25	197	23	1·7
3	21	213	19	1·9
4	17	211	17	1·8
5 and over	11	217	11	1·7

can be seen that all the coefficients of correlation are negative, but with the exception of β/α lipoprotein ratio in pipe smokers and non-smokers the trends are not statistically significant.

TABLE IV.—*Correlation Between Serum Lipids and Smoking in the Entire Sample*

	Serum Cholesterol (mg./100 ml.)	Serum Lipoproteins β/α Ratio
Cigarette smokers and non-smokers ..	−0·07	−0·10
Pipe smokers and non-smokers ..	−0·14	−0·33*
Tobacco index	−0·01	−0·11

* $P<0·001$; none of the other statistics are significant at the 5% level.

Bronte-Stewart (1961) believes that the proved relationship between serum cholesterol and cigarette-smoking in younger men may be due to dietary preferences. It is possible that these old people living on pensions cannot afford to smoke heavily and to eat well, and therefore a comparison was made between the dietary indices and some other characteristics of, on the one hand, the heavy smokers of both cigarettes and pipe tobacco and, on the other, the non-smokers (Table V). It can be seen that the heavy cigarette-smokers are significantly younger than the other two groups—a finding which reflects the difference between the smoking habits of the generation which reached maturity before and after 1914. In the sample as a whole there was a significant negative regression of serum cholesterol with age of 1.7 mg./year (Acheson *et al.*, 1958), but, even allowing for this, the differences between the mean serum cholesterol values are not significant at the 5% level. The dietary index used in this study does not measure preferences, but it has already been shown above that there is reason to believe that it measures the general level of nutrition and therefore would show whether the heavy smokers go without food. The analysis in Table V indicates that this is not the case; indeed, the heavy pipe-smokers eat rather more than the non-smokers, although the difference is not quite significant ($t=1.69$; $0.1>P>0.05$).

TABLE V.—*Serum Lipids, Age, and Dietary Index of Non-smokers and Heavy Smokers of Cigarette and Pipe Tobacco*

	No.	Age in Years		Cholesterol (mg.)		β/α Lipoprotein Ratio		Dietary Index	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Non-smokers	38	72·4	5·1	214·5	42·9	2·0	0·4	7·1	3·6
30 cigs./day or more	8	67·7*	1·9	205·7	37·3	1·8	0·3	7·0	2·3
5 oz. pipe tobacco/ week or more ..	11	72·3	4·1	216·8	65·0	1·7	0·3	9·4	4·9

* Significantly younger than the other two groups ($P<0·02$); no other group differences are significant at the 5% level.

Discussion

There can be little question of the relationship between serum lipids and cigarette-smoking in middle-aged men. It has been demonstrated in the U.S.A. (Gofman *et al.*, 1955; Thomas, 1958; Dawber *et al.*, 1959), Finland (Karvonen *et al.*, 1959), and South Africa (Bronte-Stewart, 1961), yet in the present data based on old men there is no evidence whatsoever of such a relationship—in fact, there is a suggestion that non-smokers may have a mean serum cholesterol and β/α lipoprotein ratio which are higher than in smokers.

Bronte-Stewart (1961) believes that the reason serum lipids are raised in younger smokers is because taste preferences induce them to eat more cholesterologenic substances, such as saturated fats, than non-smokers; he has published some evidence, which he does not claim to be conclusive, to support his view (Bronte-Stewart, 1961; Perrin *et al.*, 1961).

The lack of correlation between serum lipids and smoking habits in the present sample receives indirect support from the fact that smoking does not seem to be associated with coronary heart disease in them (Acheson, 1961) or in two other samples of men over the age of 65 years (Hammond and Horn, 1954; Doll and Hill, 1956). On the present evidence it is not possible to give a reason for this, even less to explain the possibility of an inverse relationship, but several theories suggest themselves. First, as has been stated, limited financial means might have caused those who smoke more to eat less, but in the present sample there was nothing to suggest that means were so limited nor that heavy smokers ate less. Secondly, if we accept Bronte-Stewart's basic hypothesis, it could reasonably be argued that the effect of ageing on the sense of taste may be more powerful than any effect of tobacco-smoking, so that the latter is obscured among old people. Thirdly, it could be that with increasing age the pattern of metabolism of fats and lipids is changed.

Our finding, although difficult to explain, is compatible with our knowledge of the aetiology of coronary heart disease in old men. In younger age-groups the greater part of coronary disease takes the form of infarction caused by thrombotic occlusion of a major vessel, a lesion which has repeatedly been shown to be associated with high serum cholesterol and a raised β/α lipoprotein ratio. Bronte-Stewart (1961) believes that the relationship between cigarette-smoking and such disease is due to the raised serum cholesterol which smokers have, rather than to any pharmacologically induced response smoking may elicit from the cardiovascular system. Only 9% of the present series had myocardial *infarction*, and in them the serum cholesterol and β/α lipoprotein ratios were raised; the remaining 81%, the majority of whom had angina pectoris and/or myocardial ischaemia, did not differ from the controls in their smoking habits or their serum lipids or serum cholesterol. Dawber *et al.* (1958), in a longitudinal study of younger men, have shown that, although cigarette-smoking and high serum cholesterol predispose to coronary thrombosis, neither predisposes to new cases of coronary heart disease presenting as angina pectoris. In line with this is the failure of Paterson *et al.* (1956) to demonstrate a correlation between cholesterol levels during life and the extent of atherosclerosis at necropsy. Our present finding, therefore, is consistent with the view already expressed (Acheson, 1961) that coronary heart disease which presents as angina pectoris and electrocardiographic evidence of myocardial ischaemia without infarction in old men is of different aetiology from acute coronary thrombosis, which is the more usual form the disease takes in younger men.

Summary

It is shown in a random sample (221) of a defined population of men aged 65–85 years that tobacco-smoking, whether in pipes or cigarettes, is not associated with elevation of the serum cholesterol or the β/α lipoprotein ratio. The significance of this finding in the aetiology of coronary heart disease is discussed.

We are again pleased to acknowledge our gratitude to the directors of Messrs. Arthur Guinness Son and Co. Ltd.

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METHODS OF DIAGNOSING CERVICAL CARCINOMA-IN-SITU

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All gynaecological patients in our unit since 1951 have been screened by the method of exfoliative cytology. Since 1958, with an increase in the number of technicians able to share the microscopical work, we began to screen all antenatal patients, so that we have now some idea of the place of cytology in clinical practice. The basic use of cytological screening is that it leads to a diagnosis of carcinoma-in-situ which is beyond our usual clinical methods; that is to say, speculum examination shows no sign of the disease at routine gynaecological examination (Papanicolaou and Traut, 1943).

Many clinicians would like to search for carcinoma-in-situ, accepting as we do that it is a curable precursor of invasive carcinoma, but they lack funds to pay for the technical help or the time to carry out the pains-taking microscopy on which the success of exfoliative cytology rests. On the other hand, there are clinicians who do not yet screen their patients, since they believe that the case for the removal of carcinoma-in-situ and the subsequent reduction in the incidence of invasive carcinoma in the community has yet to be made out. They concede, however, that for the individual woman with carcinoma-in-situ it is best for her to have it cured at once. There is no clinician in this country or elsewhere who has the temerity to watch known carcinoma-in-situ of the cervix for an indefinite period.

We would refer the clinician who is considering the use of cytology to the excellent studies of Ericson *et al.* (1956) in the U.S.A., and to the even more impressive long-term studies in British Columbia by Fidler, Boyes, and Lock (1957). From the Canadian studies it would seem to us that the case for cytology as an obligatory examination is clearly made out, and Boyes and his colleagues in British Columbia can now offer (via 1,100 family doctors) a cytological test at regular intervals to patients without gynaecological symptoms, *and at present 22% of sexually mature women have the test regularly* (Boyes, 1961, personal communication). A recent survey of the incidence of invasive carcinoma of the cervix in British Columbia shows a fall of 21%, and this reduction is thought to result from the surgical cure of carcinoma-in-situ. Naturally this fall is unlikely to continue to the complete elimination of cervical carcinoma, but, with cytological tests accepted by more and more women, many will be protected from carcinoma by its removal in its "pre"-stage. Moreover, apart from explosive rapidly growing carcinoma, cytology tests should tend to bring the patient with carcinoma for treatment at an earlier and more curable stage; but this is a less important function of cytology.

From our own experience and with the therapeutic experience of Boyes and his colleagues now available, *we feel that it must be accepted that nowadays no gynaecological or obstetrical examination is complete without cytology*. The financing of a cytology service for women without symptoms must be discussed in each community and by the National Health Service, for cytology is expensive. It is, however, very cheap when compared with the cost of treating carcinoma with its dreadful mortality and morbidity. Apart from hospital patients, intelligent women in possession of the facts will wish to have the protection provided by cytology. Given time and careful propaganda many women who have come to regard the prophylaxis of antenatal care or even poliomyelitis as commonplace will come to accept cytology "as a routine health examination not really much different from an annual visit to the dentist" (McLennan, 1958).

Our Experience with Cytology

We have already reported our experience of the technique in gynaecological practice (McLaren, Taylor, and Attwood, 1956, 1958) and also when applied to special groups such as diabetics (Noble and Attwood, 1958). We can summarize as follows: from routine cytological screening of gynaecological out-patients we expect (*a*) cervical carcinoma-in-situ in 3 to 4 per 1,000, (*b*) carcinoma of cervix missed at routine clinical examination in 1 per 1,000, and (*c*) carcinoma of the corpus not obvious in out-patients—for example, in menorrhagia in the fourth decade—in about 1 per 1,000. In round figures, 1 in every 200 is a "cytological pick-up"—that is, a diagnosis resulting from reassessment of a patient's condition prompted by the finding of cells regarded by a trained technician as sufficiently like cells from carcinoma or carcinoma-in-situ to justify biopsy studies.

Finally, there are a group of cytology findings which are not yet fully understood but which are at present being studied; the label given to these cell smears is "dyskaryosis," where certain nuclear appearances resemble those found in malignancy. We have evidence that patients who produce this type of cell must be

followed up closely and over long periods, and already we have observed dyskaryotic cell smears transformed to "positive," leading to the histological proof of carcinoma-in-situ.

In summary, then, cytology will net a "positive" in at least one out of every 200 out-patients, which we consider is a reasonable score to be set alongside many hours of microscopy with normal findings. The key to the technique is the skilled cyto-technician, who in our unit is a medical technician who carries out this work as part of his or her general duties.

Improving Our Score

The incidence of carcinoma-in-situ apparently varies with race (Scott, 1960) and probably with such factors as age, and the age when married and when pregnant. Our figure of between three and four cases of carcinomata-in-situ of the cervix per 1,000 out-patients is about average in the world literature, but, like all workers in this field, we had a desire to know if this figure represented our maximum, and also if the application of multiple screening techniques might improve our score (or "pick-up" rate). The incidence of carcinoma-in-situ, the absolute figure, will never be known without routine cervical amputation and histological studies carried out in many thousands of women from all levels of society. Accepting this fact, we set out to apply not only the aspiration of cells from the vaginal pool (a test with which we were familiar) but also two further methods known to be effective in revealing carcinoma-in-situ: (1) scraping the cervix with a simple wooden throat spatula after the method of Ayre (1947), and (2) routine biopsy of the squamo-columnar junction of the cervix (Schiller, 1928, 1938; Younge *et al.*, 1949; Younge and Kevorkian, 1959).

Not every cervix can be subjected to biopsy in gynaecological practice, and certainly not in obstetrical practice, without asking too much from patient and staff. At least in our busy out-patient department, without a large staff of assistants and with the need to teach and consult, routine biopsy of all cervices as a screening method for carcinoma-in-situ is not feasible. We therefore limited biopsy to theatre patients prior to operation or minor procedures such as dilatation and curettage.

Comparison of Scrape and Aspiration Tests

Obstetrics (mainly first trimester).—Consecutive antenatal patients, 1,500; (1) positive scrape test—proved carcinoma-in-situ, 4; positive aspiration tests—proved carcinoma-in-situ, 1. To this procedure we add cytology tests marked as "dyskaryotic" or from a clinician's viewpoint "very suspicious," an indication for cone-biopsy of the cervix—namely, (2) scrape test "very suspicious," 2; aspiration test "very suspicious," 0.

Gynaecology.—Consecutive gynaecological out-patients, 4,000; proved carcinoma-in-situ, 13; positive scrape tests, 13; positive vaginal aspiration tests, 9.

At present, therefore, the information obtained from scraping 1,500 pregnant cervices is as follows: carcinoma-in-situ, 4; atypical hyperplasia, 2. In contrast, with aspiration tests alone we should have recorded only one carcinoma-in-situ. The difference cannot, we think, be explained by a failure of technique, for the cytology team responsible, working under the direction of one of us (M.E.A.), is very experienced.

In *gynaecology*, of 13 cases of carcinoma-in-situ diagnosed as a result of positive scrape cytological tests, aspiration alone would have missed four in a series of 4,000 consecutive out-patients.

In neither obstetrics nor gynaecology was there any advantage in applying *both* aspiration and scrape tests, for on no occasion was the aspiration test positive when the scrape test was negative. There was therefore no case for using both tests as suggested by Song *et al.* (1958) in their extensive field surveys carried out in Rhode Island.

Routine Biopsy

Although we have had experience of biopsy of the post-natal cervix (McLaren, 1952), its routine use for the pregnant or gynaecological patient presents formidable difficulties. For the purpose of comparing a small punch biopsy or biopsies with a scrape-smear and with aspiration cytology we subjected a group of 770 anaesthetized women to biopsy just prior to operation. We excluded obvious carcinoma and also patients giving a positive smear, for which our routine practice is immediate cone-biopsy. We used no ancillary aids such as binocular magnification to locate the site of biopsy (Hinselman, 1925; Navratil *et al.*, 1958), but iodine-staining of the glycogen-bearing epithelium of the portio was used as advocated by Schiller and more recently by Paul Younge. Targets for biopsy were: (1) any "raw" areas extending out from the portio, a so-called erosion; (2) any obvious defect in the squamous epithelium of the portio; and (3) any pale area failing to take up iodine-staining. In all, 972 punch biopsies were taken from 769 women, the bulk of them from the squamo-columnar edge of the cervix. A single biopsy was performed in 623, two biopsies were performed in 111, three biopsies in 13, and four biopsies in 22.

The histology was read by one of us (H.C.M.) first of all without and then with full clinical and cytological notes on each case. It is not proposed here to make a detailed report on classification of the histology but simply to answer one question, "Was there any occasion when carcinoma-in-situ was diagnosed by punch biopsies in the presence of a negative cell smear?" The answer was clearly in the negative, so that we concluded from this small pilot study that routine punch biopsy had nothing to add to routine scrape smears taken from the ectocervix.

Comment

The obvious advantage of the scrape test is that it is easy to perform and never causes more than trivial bleeding (a not uncommon result of a punch biopsy). The "geography" of carcinoma-in-situ has been depicted by several workers (Foote and Stewart, 1948; Galvin *et al.*, 1955); from these studies it appears that a single (random) squamo-columnar biopsy of the cervix may well miss carcinoma-in-situ, but that four biopsies around the squamo-columnar junction are likely to be successful. This observation is obviously important, for most of our biopsies were, in fact, single squamo-columnar biopsies. Nevertheless, we had in mind the practicability of routine biopsy of the cervix in our gynaecological practice, having studied with great interest the report on cervical biopsies taken by Younge *et al.* (1949), who were able to collect 131 carcinoma-in-situ specimens before the days of the routine cytology at the Free Hospital for Women in Boston. These authors did not use colposcopy

or colpo-microscopy to locate their biopsies, although the work of Grünberger (1951), Grünberger and Antoine (1956), and Navratil *et al.* (1958) makes it clear that these methods greatly enhance the chance of a biopsy including pathological tissue.

Summary

Aspiration cell-smears were compared with scrape tests and a limited series of cervical biopsies in their ability to reveal the presence of carcinoma-in-situ proved by biopsy. The most effective method is the Ayre scrape-smear, which can be used alone since there is no overlap with either the aspiration technique or biopsy.

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The importance of diagnosing impaired hearing in young children at as early an age as possible so that the appropriate medical and educational measures can be instituted has been emphasized in guidance issued jointly by the Ministries of Health and Education to local health and education authorities, hospital authorities, and executive councils. Local authorities are asked to review the adequacy of the methods of finding cases of impaired hearing through their maternity and child welfare and school health services; to consult with local medical committees on arrangements for co-operation with general practitioners to ensure a comprehensive system of early ascertainment; and to examine with hospital authorities and local medical committees the arrangements for babies born in hospital. Children considered to be "at risk" are infants with a family history of deafness, and those known to have been subjected to any adverse pre-natal or perinatal influence; children with congenital abnormalities, multiple handicaps, cerebral palsy, and speech defects; and all retarded children.

ACUTE ALCOHOLIC HEPATITIS

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[WITH SPECIAL PLATE]

"One may drink wine and be nothing the worse for it; on another, wine may have effects so inflammatory as to injure him both in body and mind."—SAMUEL JOHNSON (1776).

Severe jaundice is regarded as an ominous event, indicative of impending death, in the chronic alcoholic patient with cirrhosis. Thus in a series of 386 patients with cirrhosis, 65% of whom were jaundiced at some time, Ratnoff and Patek (1942) found that half of the 168 who died jaundiced did so within two months and 85% within a year of the onset of jaundice: and among the alcoholic cirrhotic patients of Boston reported by Summerskill and his colleagues (1960) 11 out of 18 were deeply jaundiced at death and only 4 out of 35 recovered from severe jaundice.

Severe jaundice may, however, occur in alcoholics at an earlier stage, and before cirrhosis is established, when it is accompanied by marked constitutional disturbances —fever, anorexia, abdominal pain, nausea, and vomiting. The liver is enlarged and tender, and shows histologically acute inflammatory changes in addition to those of any underlying condition. The illness tends to run a protracted course, often ends fatally, but is potentially recoverable with suitable treatment.

Jaundice has long been known to follow alcoholic excesses (French, 1912; Hurst, 1934, 1938, 1941; Bocca, 1936), and earlier writers attributed some cases of "acute necrosis of the liver" to an excess of alcohol (Osler, 1892; Rolleston and McNee, 1929). Few other reports of severe jaundice in alcoholics (Davis and Culpepper, 1948; Welin, 1950; Eckhardt *et al.*, 1950) appeared before the importance of acute hepatic insufficiency in chronic alcoholics was stressed by Phillips and Davidson (1954), all of whose 56 patients had drunk heavily before the jaundice developed. These authors assigned a bad prognosis to the condition, many of their patients dying and the remainder showing varying degrees of slow and mainly incomplete recovery. They described a histological picture which they believed to be characteristic and which will be described later. Of 28 patients with the characteristic lesions, 18 died, as did 10 of 13 with severe jaundice.

The object of the present paper is to emphasize the recognition and treatment of this condition, which have received scant attention in the literature of Great Britain. Seven cases of acute alcoholic hepatitis investigated by the authors at the Royal Free Hospital since 1953 are considered, though other such cases were treated in the hospital during that time.

Clinical and Pathological Findings

One case is reported in full below, while the remainder are summarized in Tables I–III.

Case 5

A brewer's drayman aged 45 was first admitted to hospital in September, 1958, with a spontaneous pneumothorax, when the liver was enlarged 4 cm. below the costal margin, but not tender. For about two years he had had a poor appetite, which became worse in the previous two months. He had lost about 1½ stones (9.525 kg.) in weight in four years. Some days he ate no food at all, but drank 6 or 7 pints (3.5 or 4 l.) of beer. At times he had cramps in his legs at night, and these he associated with periods of excessive drinking. For two years he had noticed tremors of the hands. Results of liver-function tests were within normal limits, though the serum albumin level was 3.3 mg. per 100 ml.

He was readmitted to hospital six months later because of jaundice, the duration of which was uncertain. It had undoubtedly been present for three months, during which time the urine had been dark, though the stools had become pale only shortly before admission. There had been marked anorexia for two months, but no nausea or abdominal pain. He denied alcoholism, but later said he had drunk 10 pints (5.68 l.) of beer daily for years and that he had changed to gin after the first admission to hospital. He was unkempt, apathetic, and clinically anaemic; the temperature was 100° F. (37.8° C.); he was thin, jaundiced, and showed a fine non-flapping tremor of the outstretched hands; there was slight palmar erythema; spider naevi were present on the cheeks; the liver edge was tender and palpable 8 cm. below the costal margin.

Investigations.—Results of laboratory investigations are shown in Table IV. On the seventh day the mean cell volume was 120 c.μ, the mean cell haemoglobin concentration 27.7%, and the colour index 1.12. The serum iron level was 180 μg. per 100 ml.

Progress.—Treatment was started with a high-carbohydrate, low-protein, low-fat diet and large dose of aneurin parenterally. Slight lessening of jaundice and improvement in the biochemical findings ensued, but the fever (99°–100° F.; 37.2°–37.8° C.) and jaundice persisted. A superior vena caval drip of 50% glucose solution was started on the 12th day after admission. Three days later jaundice was fading and in a week the temperature subsided to normal, and by

TABLE I.—*Relevant History and Symptoms*

Case No.	Age and Sex	Duration of Acute Illness (Before Admission) (Days)	Duration of Anorexia	Duration of Chronic Alcoholism and Main Drink	Epigastric Pain	Previous Attacks of Jaundice	Known Duration of Fever in Hospital (Days)	Presence of Nausea and Vomiting	Total Time in Hospital (Days)
1	38 F	21	2 years (intermittent)	2 years; spirits	Severe	"Infective hepatitis" 4 years before	14	Yes	13
2	48 M	4	10 days	12 years; spirits	Absent	× 3 after drinking bouts in last 3 years	21	,,	21 (self-discharged)
3	39 M	14	14 ,,	2 years; spirits	Severe	"Infective hepatitis" 10 years before	35	,,	112
4	40 M	5	1 year (intermittent)	1 year; spirits	,,	"Infective hepatitis" 15 years before	28	,,	68
5	45 M	14	2 years (intermittent)	5 years; beer, latterly spirits	Absent	None	21	No	50
6	49 M	28	28 days	10 years; beer and spirits	Severe	,,	28	Yes	28 (self-discharged)
7	55 F	7	35 ,,	20 years; spirits	,,	,,	14	,,	36

TABLE II.—*Main Clinical and Biochemical Features*

Case No.	Liver Enlargement (cm. below R. Costal Margin)	Spleen	Spider Naevi	Palmar Erythema	Signs of Vitamin-B Deficiency	Ascites	Oedema of Ankles	Max. Serum Bilirubin (mg./100 ml.)	Serum Albumin (Lowest Figure) (g./100 ml.)	Prothrombin Concentration (%)	Serum G.O.T. in First Week	Highest Alkaline Phosphatase (K.A. Units/100 ml.)	Highest Neutrophil Count in 1st Week (per c.mm.)	Cerebral State
1	4 cm.; tender	0	0	0	0	+	+	4·2	2·2	—	—	26·0		Delirium
2	8 cm.; tender	+ 2 cm.	0	0	0	0	+	2·0	3·7	—	—	29·5		,,
3	7 cm.; tender	0	0	0	0	0	+	19·0	2·6	41	—	25·0	12,000	,,
4	6 cm.; tender	0	0	0	Cerebral beriberi	0	0	10·0	2·7	43	96	20·0	3,500	Wernicke's encephalopathy
5	8 cm.; tender	0	+	+	0	0	+	8·0	2·4	60	135	27·0	14,250	Confusion
6	12 cm.; tender	+ 2 cm.	+	+	0	+	+	22·0	3·1	42	20	17·0	8,800	Normal
7	6 cm.; tender	0	+	+	0	0	0	8·5	3·4	60	168	39·0	3,500	Confusion

TABLE III.—*Summary of Histological Findings*

Case No.	Type of Specimen	Phase during which Examined	Cirrhosis	Portal Scarring	Fat	Mallory's Hyaline	Cellular Degeneration and Necrosis	Bile Stasis	Acute Inflammation	Bile-duct Hyperplasia
1	Biopsy	Acute	+	+	+	+	+	+	+	+
	P.M.	After treatment	+	+	±	+	0	0	0	0
2	,,	,, ,,	+	+	+	0	0	0	0	+
3	None									
4	Biopsy	Acute	+	+	+	0	+	+	+	+
5	,,	,,	0	+	+	0	+	+	+	+
	,,	After treatment	0	+	±	0	0	0	0	0
6	,,	Acute	+	+	+	+	+	+	+	+
	,,	After treatment	+	+	±	0	0	0	0	0
7	,,	Acute	0	+	+	0	+	+	+	+

TABLE IV

Investigation	Week of Admission					
	1	2	3	4	6–7	12+
Total serum bilirubin (mg./100 ml.)	8·0	2·4		1·8	0·2	0·7
Serum albumin (g./100 ml.)	2·6	2·4	3·1	2·8	4·1	3·9
,, globulin (g./100 ml.)	2·7	2·8	3·4	3·4	3·0	2·9
Thymol turbidity (K.A. units/100 ml.)	1			2		3
Serum alkaline phosphatase (units/100 ml.)	27	14	11	10	14	11
Prothrombin concentration (%)	60	60	60	100	100	
Serum glutamic–oxalacetic transaminase (units/100 ml.)	135	49	28			20
Blood urea (mg./100 ml.)	24	12	28	13	17	
Total W.B.C. (per c.mm.)	11,200	17,600	11,700	12,800	12,100	
Neutrophils (per c.mm.)	8,288	14,250	7,956	8,700	7 190	
Hb (g./100 ml.)	8·3	8·3	14·2	14·8	15·1	16·3
Hb percentage	57	57	97	101	108	112

the 21st day he was well enough to be allowed up. The anaemia (Hb 8.3 g. per 100 ml., with macrocytosis) was corrected by blood transfusions. He was discharged after seven weeks in hospital.

After ten weeks biochemical tests showed great improvement, as did the histology of the second biopsy.

When last seen, in July, 1959, the patient was well and gaining weight, but was drinking again despite warning of the consequences.

Histology.—The first biopsy ten days after admission showed a portal fibrosis with no marked change in the liver architecture and with moderate fatty change. The liver cells showed no Mallory's "alcoholic hyaline" reticulum, but contained glycogen as well as fat. Intralobularly there were many foci of degenerate cells, often infiltrated with leucocytes, which were mainly polymorphonuclears, but mononuclears and eosinophils were also present; in some areas whole lobules appeared to be degenerating, simulating the appearances of massive necrosis. Bile stasis and thrombi were very prominent. The portal triads showed stellate scarring and marked bile duct hyperplasia, and were heavily infiltrated with leucocytes of all types; they were oedematous.

The second specimen, taken about three months later, showed considerable improvement; the fat had almost disappeared, as had the acute inflammatory cellular infiltration. The disappearance of the fat was associated with increase in cytoplasmic granules and a very mild bile stasis (no thrombi). There was no evidence of hepatocellular degeneration or necrosis, but there was increase in cellular polyploidy. The triads showed residual scarring, but no acute inflammatory changes. Reticulin stains showed an apparent increase and consolidation of the fibrosis, but this was due to the collapse of a reticulin network formerly distended by swollen cells and to inflammatory oedema.

In summary, the biopsy after three months' treatment revealed a loss of fat, bile stasis, and hepatocellular degeneration, with disappearance of the acute inflammatory reaction, leaving some residual scarring of the portal tracts.

Summary of the Histological Appearances of Seven Cases

Basically, there appears generally to be evidence of previous damage extending from a mild chronic inflammation and stellate scarring of the portal tracts, with no disorganization of architecture, to a frank cirrhosis with nodular hyperplasia. Superimposed upon these chronic changes of pre-cirrhosis and cirrhosis there is evidence, in the acute exacerbations, of focal (Special Plate, Fig. 1) and massive cellular degeneration and necrosis, marked fatty change and bile stasis (Special Plate, Fig. 2), and a reactive bile-duct hyperplasia with an acute inflammatory reaction (Special Plate, Fig. 3)—the so-called alcoholic hepatitis. These acute changes may disappear after treatment (Special Plate, Fig. 4).

Mallory's "alcoholic hyaline" reticulum was not an invariable finding in these cases of alcoholism, only two cases showing the lesion. In one patient who recovered the hyaline reticulum appeared to have disappeared completely; in another, though the acute inflammatory reaction had disappeared, as had most of the fat, the presence of the hyaline reticulum in the cells had increased in amount at the time of death.

Discussion

Commentary on the Seven Cases

The more constant features of this illness need emphasis, as it may be mistaken for infective hepatitis or for surgical jaundice, even when cirrhosis is known to be present. Six of the patients were from the professional middle class, a fact in keeping with the cost of alcoholic drinks in Britain. Only one of our patients admitted not eating enough food; he was a brewer's drayman (Case 5) who, unable to afford both, lived increasingly on alcohol. Welin (1950) noted the same social and dietary aspects in Scandinavia. In America the majority of similar cases described come from the ranks of unemployed, unskilled or semi-skilled, who commonly are observed to have nutritional deficiencies (Summerskill *et al.*, 1960). All our patients had increased their drinking excessively just before their illness; three patients, returning from overseas, reported increased consumption of alcohol at farewell celebrations immediately preceding the onset of jaundice, and a fourth drank more heavily than usual over Christmas. The patient in Case 2, the only true dipsomaniac of the group, had precipitated several attacks of jaundice by his debauches. All the patients were long-standing drinkers of spirits (regularly one bottle of spirits and often much more daily), except Case 5, and his illness coincided with a change from beer to gin. The condition also may develop in beer-drinkers (Ratnoff and Patek, 1942; Summerskill *et al.*, 1960).

Some scepticism is advisable in accepting personal accounts of alcoholic intake of these patients—for example, because of mental impairment at some stage of the illness (Cases 1–5 and 7), and also because social as well as clinical accounts of alcoholic consumption tend to err greatly to the side of understatement (Welin, 1950; Klatskin, 1959). It is unlikely that any really accurate records of the consumption of food and drink by the alcoholic have yet been obtained. The majority of these patients did not volunteer information about the amount of alcohol they drank, and three in this series, when first asked specifically about it, denied that they did so at all. Similar experiences are reported by Welin (1950) and, particularly in women, by Summerskill *et al.* (1960).

Four patients had had previous single attacks of jaundice, diagnosed as "infective hepatitis," from 4 to 16 years before the illness described here. Though only one was known to be actively alcoholic at the time of the first attack of jaundice, three others were probably already heavy drinkers. In published series antecedent jaundice in such cases is comparatively rare.

The onset of the illness was acute in four cases, but more insidious in the others. Jaundice had been noted for a week or less before admission in four, and from three weeks to four months in the others.

The outstanding single symptom of these patients was anorexia, which preceded the jaundice in each by a widely varying interval, and may have marked the onset of liver dysfunction irrespective of when the jaundice subsequently occurred. At some stage in all these cases it became so severe as to induce total abstinence—an important feature of successful treatment. Persistent epigastric pain was a striking feature in three cases, and was only partially relieved even with strong analgesics. With anorexia four had severe nausea and vomiting. Liver enlargement and hyperaemia of the stomach were presumably responsible for these symptoms, though they may have been early manifestations of Wernicke's encephalopathy.

As in other series (for example, Phillips and Davidson, 1954 ; Summerskill *et al.*, 1960) this illness was invariably accompanied by fever, sometimes high ; here in all cases the fever lasted at least two weeks after admission, and in five it persisted for up to four weeks. This contrasts with the temperature pattern usual in infective hepatitis, where the temperature commonly falls with the appearance of the jaundice.

All these patients had a tender liver, enlarged in varying degrees ; in one case (No. 6) it was palpable well below the umbilicus. Only in two cases was the spleen palpable ; two had ascites and oedema, and three had some of the stigmata of chronic liver disease.

Though vitamin-B deficiency has been widely implicated as an aetiological factor in cirrhosis in this series, only one patient showed clinical evidence of vitamin-B deficiency on admission ; but the precipitation of Wernicke's encephalopathy in Case 4, and possibly in Case 3, by diarrhoea, high-carbohydrate diet, and inadequate vitamin-B therapy suggested a latent deficiency in these patients.

Mental impairment, varying from apathy, inattention, and depression to frank delirium, occurred at some stage in six patients ; in three the response to aneurin indicated deficiency of this vitamin to be the underlying cause.

Laboratory investigations, usually valuable as diagnostic aids in jaundiced patients, were only of limited or negative value in the present series, in the last five cases of which they were most comprehensively carried out. The so-called " liver-function test " suggested liver-cell damage with some intrahepatic obstruction rather than a primarily extrahepatic type of jaundice, but in the most severely ill patient (Case 3) the tests for hepatocellular degeneration never gave strikingly abnormal results. There were high serum bilirubin values in Cases 3 and 6 (19 and 22.5 mg. per 100 ml. respectively), in both of which recovery took place. A low serum albumin level was found at some stage in Cases 1, 2, and 5 ; though this is generally regarded as a poor prognostic feature, one of these patients made a virtually full clinical and pathological recovery. The serum glutamic–oxalacetic transaminase level was raised in three out of four cases, and fell to normal with clinical recovery from the acute stage ; in the fourth case it was not significantly raised when a severe degree of clinical and biochemical liver damage existed. The prothrombin concentration was greatly diminished in five cases, and, as anticipated, did not alter with parenteral administration of vitamin K. Welin (1950) and Eckhardt *et al.* (1950) have likewise suggested that liver-function tests may be of no positive diagnostic value in such cases. According to Ducci (1957), alcoholic cirrhosis with jaundice bears no biochemical resemblance to acute viral hepatitis ; in the former he found the enzymes normal or only slightly raised, the thymol turbidity slightly increased, and the thymol flocculation generally negative, and concluded that the jaundice in alcoholic cirrhosis is not due to a virus, but is a grave complication of the disease.

In contrast, the leucocyte count is considered to be a valuable diagnostic aid. Thus, Phillips and Davidson (1954) and Summerskill *et al.* (1960) found a neutrophil leucocytosis in the peripheral blood of all patients whose serum bilirubin was above 5 mg. per 100 ml., and the former considered it to indicate a bad prognosis. This was not so in our series, in which a neutrophil leucocytosis was present in four cases, though the very high values reported by Phillips and Davidson were not seen. A neutrophil leucocytosis, when present, is of undoubted importance in distinguishing this condition from infective hepatitis and some other types of jaundice.

Anaemia is a feature of some of these cases. Anaemia or a fall in haemoglobin concentration occurred at some stage in six cases of the present series, three of which had macrocytosis and one reticulocytosis. The pathogenesis was not fully understood, but was probably haemolytic, at least in part when haemodilution or gastro-intestinal haemorrhage, liable to be present in such cases, could be excluded. Such an anaemia is known to occur in some patients with cirrhosis without severe jaundice, as described by Jandl (1955), who demonstrated an increased rate of red-cell destruction, probably due to excessive splenic activity, in all his patients with cirrhosis, while a small proportion had severe anaemia with evidence of folic-acid deficiency. He also found a reticulocyte peak about seven days after withdrawal of alcohol, and concluded that alcohol directly or indirectly had a toxic action on the bone-marrow. Writing on a " new symptom complex," Zieve (1958) reported five alcoholic patients with acute jaundice, a transient haemolytic anaemia arising in the early stages, and hypercholesterolaemia, though the serum cholesterol of four of our patients with anaemia remained within the normal range. Froehlich (1958) had described hyperlipaemia, mainly of neutral fat, but also with a high serum cholesterol level, in acute alcoholism without jaundice.

In general, the abnormality of the biochemical values did not seem to be of direct prognostic significance, and neither did the clinical estimate of the gravity of the patient's condition. Whether this would have been so bad had the treatment been different remains an interesting but profitless speculation.

The lack of awareness of the condition of acute alcoholic hepatitis in Great Britain and the absence of diagnostic laboratory tests obviously create a danger of misdiagnosis and hence inappropriate treatment. The duration and depth of the jaundice might easily lead to surgical advice being sought primarily, especially when the jaundice is associated with upper abdominal pain and vomiting. This happened in Case 1 ; the laparotomy with drainage of ascites probably removed whatever chances of recovery the patient had. In all, three of these patients were admitted originally to surgical wards, and surgical opinion was sought early in Case 3.

Needle biopsy of the liver, with the usual precautions, seems at present to be the most valuable method of differentiating between this type of jaundice and other forms ; the histology is discussed later.

Treatment

Initial treatment should begin without delay and must depend on awareness of the condition and its early diagnosis. It is based on the removal of the presumed toxic factor, alcohol, together with rest in bed and the use of a high-calorie diet. Because of anorexia, nausea, and vomiting many of these patients may be quite unable to take the required 3,000 calories by mouth, and parenteral fluids then become obligatory. Hypertonic glucose (50%) by vena-caval drip, which can be maintained for long periods, appears to be the method of choice, and the institution of this form of therapy marked the turning-point in Cases 3, 4, and 5.

However, some improvement may take place even on a poor diet after cessation of alcoholic intake (Eckhardt *et al.*, 1950), as occurred in Cases 2 and 5. Davidson (1958) claims that normal diet is adequate for recovery, but most nauseated patients have difficulty in taking this orally.

Though most of these patients are able to metabolize moderate amounts of protein, many workers have pointed out serious consequences (liver coma, neuropsychiatric abnormalities, etc.) of high-protein diets in the presence of liver failure and porto-caval shunts (Walshe, 1951; Riddell and McDermott, 1954; Sherlock *et al.*, 1954; Summerskill *et al.*, 1956). It seems rational, therefore, to restrict protein intake, in severe cases at least, until some degree of recovery has taken place. Subsequently a high protein intake is desirable; Eckhardt and his colleagues (1950) found that this type of patient improved only to a certain point until protein was added to the diet. The emphasis on carbohydrate therapy and the theoretical probability of pre-existing vitamin deficiencies imply that vitamin B in large doses is an important adjunct; the need for this is illustrated by the occurrence of Wernicke's encephalopathy in Case 4 and probably in Case 3.

If there is evidence of portal hypertension or gastro-intestinal haemorrhage, gut sterilization by wide-spectrum antibiotics is advisable to reduce absorption of bacterial protein and perhaps to suppress the formation of other as yet unidentified products of bacterial action.

Whatever part alcohol plays in the production of the acute condition under discussion, most authorities on cirrhosis tacitly, if not openly, admit its major role by agreeing on the need for subsequent total abstinence by patients under their care, and, though recovery from the acute illness may be complete, this only marks the beginning of a long-continued supervision, wherein advice often goes unheeded and cirrhosis develops and progresses inevitably to death.

Histology

In our series the histological lesion appears to be an acute hepatocellular degeneration and fatty change proceeding to a patchy necrosis; the latter tends to evoke an acute inflammatory reaction. Both the degenerative condition and the inflammation subside after suitable treatment.

Similar findings were recorded by Davis and Culpepper (1948) in one patient studied by serial biopsies. Phillips and Davidson (1954) drew attention to the acute phase in chronic alcoholism; the changes described appear to be essentially similar to those of our series, but they went further, as they felt that they could relate the degree of inflammatory cellular reaction to the severity of the illness. Gall (1957) also found similar morphological changes in acute alcoholism which he named "toxic hepatitis." Many workers are agreed that the fatty change in the acute phase of alcoholism is indicative of hepatocellular degeneration, which may be reversible after treatment (Davis and Culpepper, 1948; Phillips and Davidson, 1954; Gall, 1957; Popper and Szanto, 1957).

There is, however, no unanimity of opinion concerning the significance of the presence of the so-called "alcoholic hyaline" reticulum regarded by F. B. Mallory (1911) as specific. Popper (1959) and Summerskill *et al.* (1960) have not seen it in non-alcoholics, whereas Baggenstoss and Stauffer (1952) have found it in post-hepatitic cirrhosis, and Steiner (1959) claims to have found it in non-alcoholics in Africa.

According to G. K. Mallory (1960), the thesis that all cells containing hyaline reticulum become necrotic is much disputed, but there is considerable evidence that the condition may be reversible. The evidence in our hands is in keeping with this statement: in Case 1 the hyaline increased after treatment despite concurrent loss of fat, and in Case 6 it disappeared.

The histological diagnosis of adequate specimens of liver obtained by needle biopsy presents little difficulty. In viral hepatitis the zonal distribution contrasts with the patchy cellular necrosis of alcoholism, and consideration of the clinical and biochemical findings will help in making a further distinction between the two. Though it has often been postulated that the two conditions may be superimposed, Popper (1957) is of the opinion that in practice the histological indications that the two have coexisted have not been recorded in the literature.

Differentiation from intrahepatic and drug-induced jaundice should prove of no difficulty, because of the absence of fatty change in these conditions.

Case 1 showed a chronic pancreatitis at necropsy; this is in keeping with the views of Shallenberger and Kapp (1958), who claimed that of all cases of pancreatitis 20% are associated with alcoholism, and of Owens and Howard (1958), who found that all the patients with pancreatic calcification seen in the Grady Memorial Hospital, Atlanta, Georgia, were advanced alcoholics. On the other hand, Pollock (1959) in Great Britain did not consider that alcoholism had any part to play in his series of cases of pancreatitis.

Aetiology

Excluding intercurrent conditions of separate aetiology, such as reactions to drugs, jaundice may develop in alcoholics in several ways: (1) as in the cases described, following excessive drinking; (2) after gastro-intestinal haemorrhage, when anoxia of a damaged liver and the increased metabolic work in dealing with the sudden increase in protein absorption appear to be responsible; and (3) as a terminal event in advanced and already irreversible liver-cell failure (often associated with gastro-intestinal haemorrhage). The last two occur at an advanced stage of cirrhosis, whereas the first may occur at any time. Minor degrees of jaundice also occur, apparently unrelated to excessive intake of alcohol in the so-called active phase of cirrhosis. A relationship between active cirrhosis and the illness described in this paper has not been estab-

lished, chiefly because of lack of reliable information concerning drinking habits. It is also not certain whether the attacks of hepatitis described here represent stages in the development of cirrhosis, or whether, with subsequent abstinence, any liver damage which has already occurred remains stationary or even resolves. Our study suggests the latter is true, though the period of follow-up is relatively short. As several of these patients were said to have had "infective hepatitis" many years previously, it is conceivable that alcohol might have reactivated the infection; a further possible explanation which has been suggested is that the illness was a primary viral hepatitis developing in a liver already damaged and cirrhotic. This is contrary to the different histological and biochemical pictures and goes against clinical experience (Popper, 1957).

Despite the long-accepted association between alcoholism, a fatty liver ("pre-cirrhosis"), and cirrhosis, no conclusive evidence exists to show that alcohol is directly responsible, and other mechanisms, such as malnutrition and vitamin-B deficiency, have been blamed. The chief difficulties in establishing such a relationship lie in the failure to produce cirrhosis regularly in animal experiments by giving alcohol, and in the relatively small proportion of human alcoholics who develop cirrhosis, estimated to be about 8% in the United States.

The fatty liver of alcoholics is usually considered to be a pre-cirrhotic condition, and its potential reversibility has been stressed (Connor, 1938; Hall and Morgan, 1939; Welin, 1950; Popper and Szanto, 1957; Klatskin, 1959), though this has been denied (Dible, 1951). Fatty infiltration of the liver was demonstrated by Ashworth (1947) to follow the ingestion of alcohol by rats in spite of adequate diet, while improvement has been observed to follow the withdrawal of alcohol (Klatskin and Yesner, 1949).

The severe illness described here seems to be more closely related to the direct toxic action of alcohol on the liver than with malnutrition. It followed closely upon alcoholic debauches, and, though the exact intake of food on these occasions is not known, most of our patients appeared to eat normally until the onset of anorexia. On the other hand, if alcohol is finally utilized as a carbohydrate, the two sharing a common pathway from the pyruvate stage, then clearly a relative excess of carbohydrate over protein existed. But if this is an aetiological factor, and an absolute excess of carbohydrate over protein has been held responsible for liver damage, it is paradoxical that a pure carbohydrate diet of 3,000 calories should have caused improvement. Similarly, it is difficult to involve aneurin deficiency, as in one case the hepatic condition improved on a regimen which itself produced cerebral beriberi. We have unpublished evidence that subicteric attacks of hepatitis may be produced by excessive drinking, and it is suggested that cirrhosis in the alcoholic may be caused by repeated minor attacks of hepatitis, clinical or subclinical, icteric or non-icteric, produced by the direct toxic action of alcohol.

Other descriptions have been used for this condition. Phillips and Davidson (1954) called it "acute hepatic insufficiency of chronic alcoholics," but they also included in this category what appears to be the terminal phase of cirrhosis, when the production of jaundice and of hepatic insufficiency is almost certainly different from that of the acute and potentially reversible stage. More recently the Boston group of workers (Davidson, 1958) have used the term "active cirrhosis" for at least some of these cases; this term implies that the cause of the acute illness and that of cirrhosis are the same. At present it is by no means certain that this is so; in addition there is no doubt that the acute condition may occur in the absence of cirrhosis.

The term "acute alcoholic hepatitis" was used by Hurst (1934, 1938) for a pre-cirrhotic state, sometimes accompanied by slight jaundice, in which complete histological recovery followed total abstinence, but he also applied it to patients the description of whose condition suggested a chronic hangover and who were never jaundiced at all. Moreover, these patients were mainly young adults, in contrast to the older age of patients of the present and similar series. Cases histologically resembling the present ones were described by Gall (1957) as "toxic hepatitis," but the term lacks specificity and indeed urgency.

The term which we prefer is "acute alcoholic hepatitis." The word "hepatitis" is not entirely satisfactory, as some of the histological changes are degenerative (as they may be in any form of inflammation) and may possibly arise from a deficiency state. On the other hand, the classic changes of acute inflammation are present, though presumably induced chemically rather than by bacteria or viruses. This name gives the impression of an acute condition which, as there seems to be no reliable prognostic guide to the eventual outcome, merits urgent and energetic treatment.

Summary

Acute alcoholic hepatitis often follows intensified drinking, usually by the chronic alcoholic, and is characterized by jaundice, which is often severe, anorexia, nausea, vomiting, upper abdominal pain, hepatomegaly, and fever. Details of seven cases are presented.

The illness described may be readily misdiagnosed as infective hepatitis or surgical jaundice even when cirrhosis is known to be present and treatment wrongly planned.

In the cases reported biochemical investigations did not show any characteristic pattern, though they suggested liver-cell damage with an additional obstructive element to the jaundice. In severe cases a neutrophil leucocytosis is present. Anaemia, possibly haemolytic in origin, commonly develops.

Histologically, there is evidence of focal and massive cellular degeneration and necrosis, marked fatty change, bile stasis, and a reactive bile duct hyperplasia with an acute inflammatory reaction. Mallory's alcoholic hyaline reticulum is not invariably present. These acute changes, which disappear after treatment, are superimposed on existing changes of pre-cirrhosis or cirrhosis.

Treatment consists of withdrawal of alcohol, rest in bed, a high calorie intake (by vena-caval drip if necessary), and large supplements of vitamin B. In the earlier stages reduction of protein intake is theoretically desirable, and with such treatment the reported high fatality rate may be lowered and liver function in some cases restored to normal. With recovery, however, the main problem, that of preventing continued alcoholism, remains.

We wish to thank Dr. Una Ledingham, who was at some stage responsible for the clinical management of six patients.

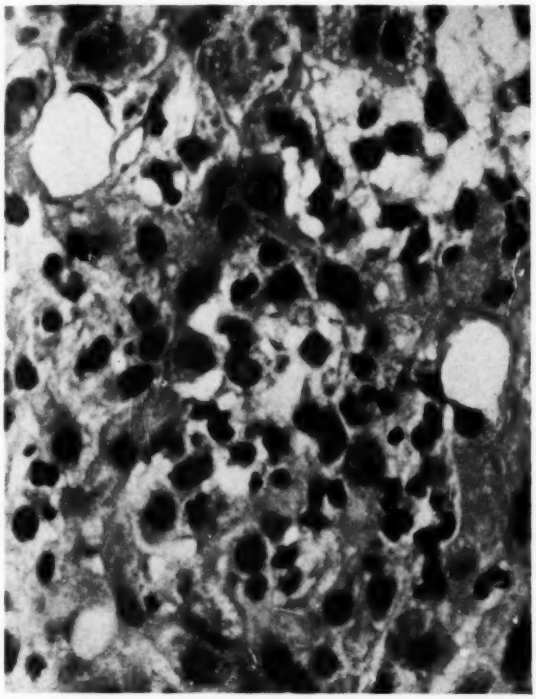

Fig. 1.—Acute alcoholic hepatitis. Focal area of cellular degeneration infiltrated with polymorphonuclear leucocytes. (H. and E. ×160.)

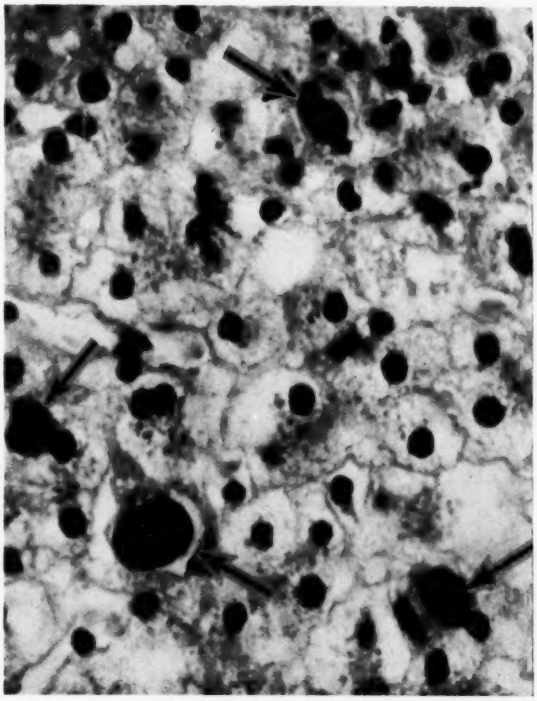

Fig. 2.—Acute alcoholic hepatitis. Bile thrombi indicated by arrows. There are considerable cellular degeneration and much granular pigment (bile stasis). (H. and E. ×160.)

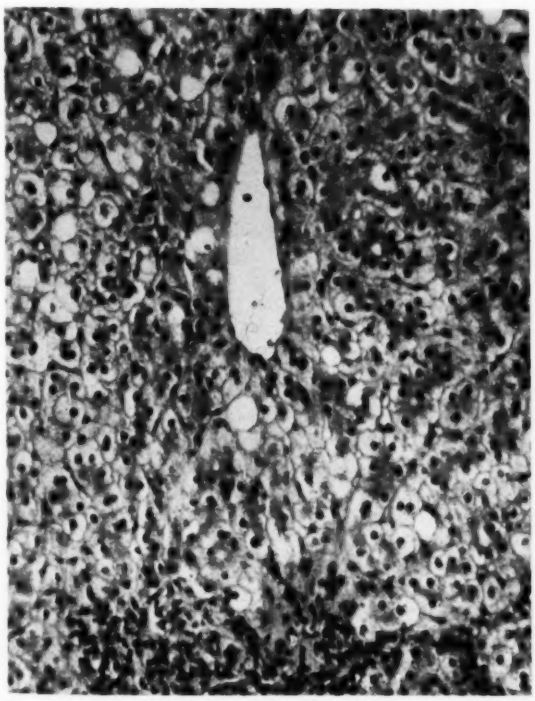

Fig. 3.—Acute alcoholic hepatitis. The cells are vacuolated and there are acute inflammatory exudates both intralobularly and portally. (H. and E. ×40.)

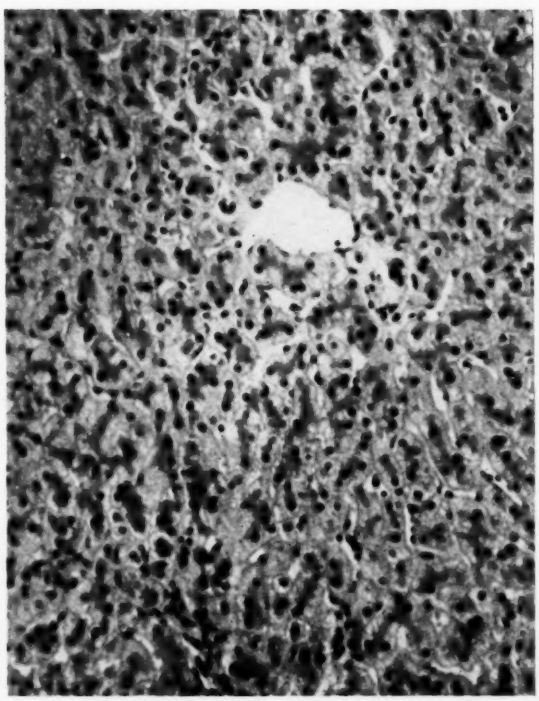

Fig. 4.—Acute alcoholic hepatitis following recovery. The same case as in Fig. 3 but 12 weeks later. Note that the inflammatory reaction has subsided and the cells are no longer vacuolated. (H. and E. ×40.)

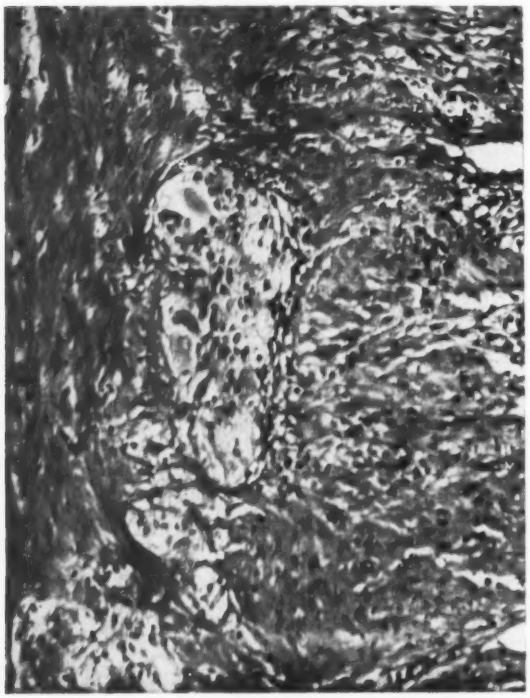

Fig. 1: Case 11.

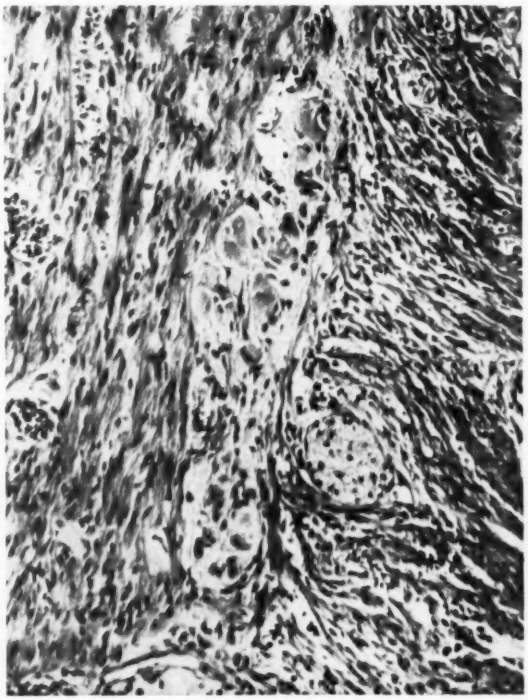

Fig. 2: Case 12.

Figs. 1 and 2.—Ganglion cells of Auerbach's plexus between muscle layers of bowel wall.

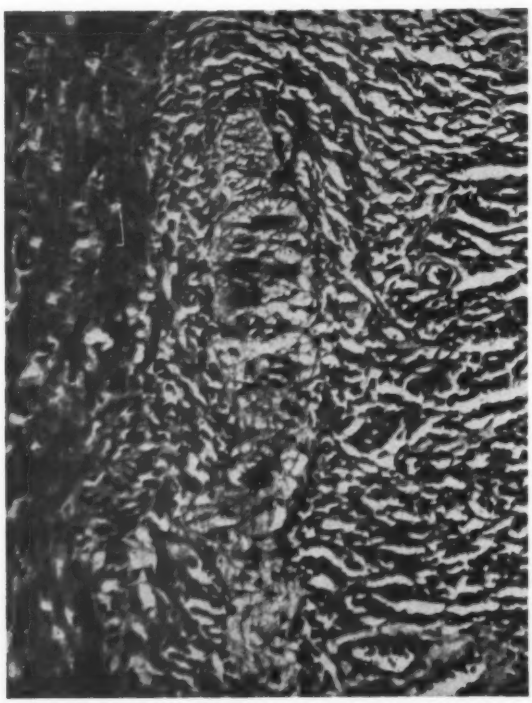

Fig. 3.—Case 14. Ganglion cells of Auerbach's plexus between muscle layers of bowel wall.

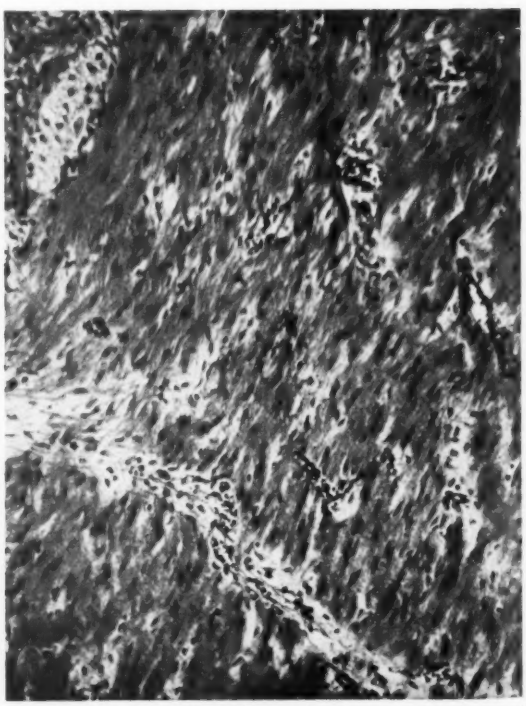

Fig. 4.—Case 10. Photomicrograph of part of bowel wall showing pale swollen muscle fibres surrounded by inflammatory exudate.

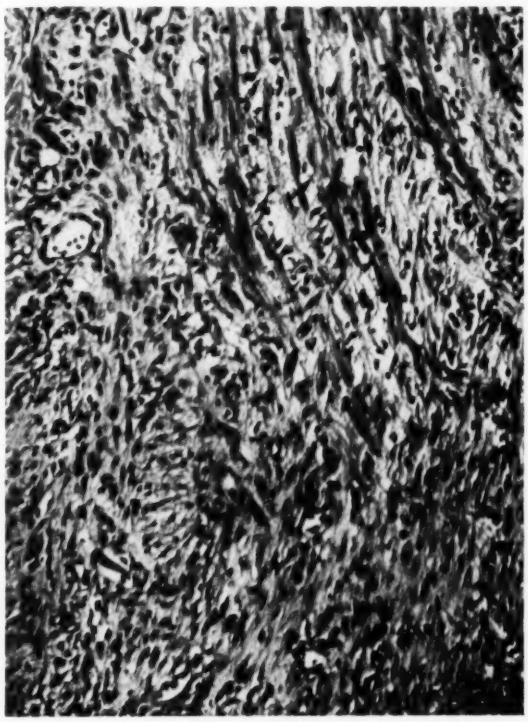

Fig. 5: Case 11.

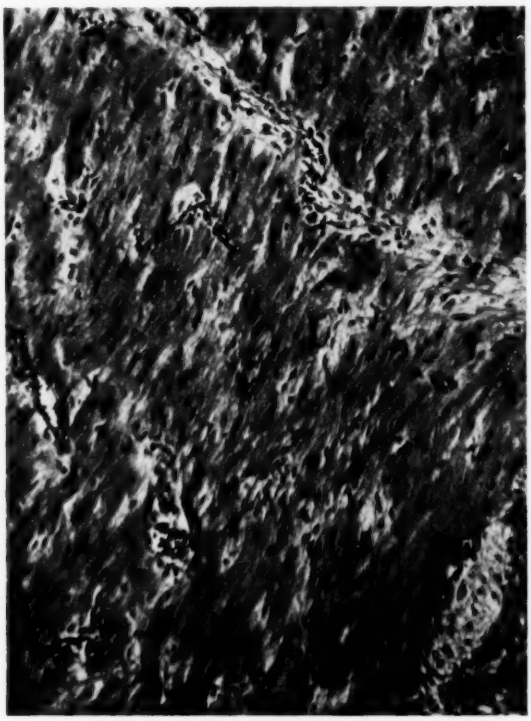

Fig. 6: Case 14.

Figs. 5 and 6.—Photomicrographs of parts of bowel wall showing pale swollen muscle fibres surrounded by inflammatory exudate.

Fig. 7.—Case 12. Straight radiograph of abdomen showing dilatation of transverse colon.

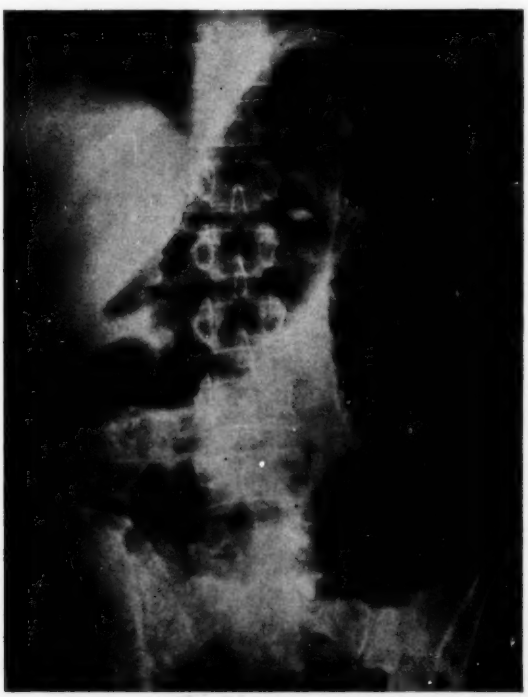

Fig. 8.—Case 5. Straight radiograph of abdomen showing the enormously dilated colon.

FIG. 1

FIG. 3

FIG. 4

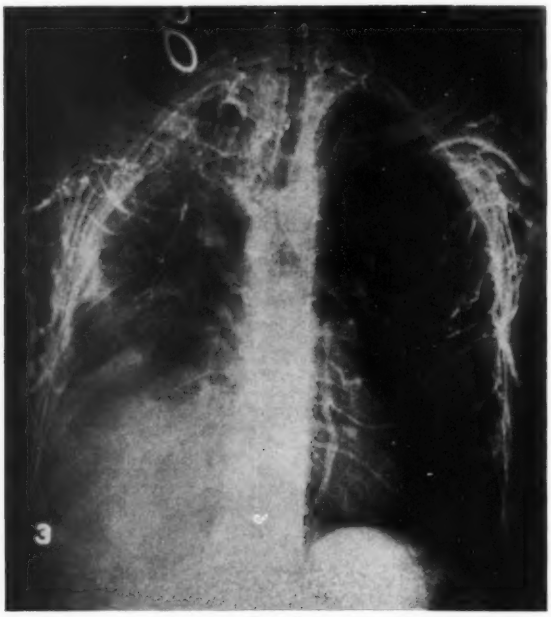

FIG. 2

FIG. 5

FIG. 1.—Case 1. Phlebogram showing complete block of both subclavian veins with collateral circulation.

FIG. 2.—Case 1. Phlebogram one month after anticoagulant therapy, showing considerable increase in collateral circulation.

FIG. 3.—Case 2. Phlebogram showing complete blockage of left innominate vein.

FIG. 4.—Case 2. Phlebogram two months after anticoagulant therapy, showing recanalization of left innominate vein and decrease in collateral circulation.

FIG. 5.—Case 3. Phlebogram showing occlusion of left subclavian and innominate veins.

for her help and encouragement to make this study; Professor Sheila Sherlock for permission to study Case 7, Dr. A. M. Ramsay for Case 3, and Mr. George Qvist for Case 6. For their willing help in the secretarial work involved we must thank Miss H. M. Haestier and Miss P. C. Wraight.

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A bilharziasis eradication project—the first of its kind in the world—is at present under way in Egypt with the assistance of the World Health Organization. The project gained priority because of the fear that the bilharziasis problem will loom larger when the Aswan High Dam is completed seven years from now. The lake that will form behind the dam will be the largest man-made lake in the world, and could become another fertile breeding-place for the parasite-carrying snails. The eradication project will strengthen existing control measures. At present there are 859 bilharziasis treatment centres in Egypt, which made it possible to detect and treat 4,000,000 cases in 1960 as against only 1,000,000 cases in 1952. (WHO/31, July 28.)

DILATATION OF THE COLON IN ULCERATIVE COLITIS

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[WITH SPECIAL PLATE]

The recognition of dilatation of the colon as a complication of ulcerative colitis has been reported infrequently; the condition can occur either in an acute first attack or in an acute relapse of a chronic ulcerative colitis. Though not mentioned in a review of the local complications in 2,000 cases seen by Sloan *et al.* at the Mayo Clinic in 1950, in 1951 Madison and Bargen reported a case of "unusual segmental dilatation" of the transverse colon without distal obstruction which occurred in a patient with a fulminating relapse of chronic ulcerative colitis of 11 years' duration. The syndrome was referred to in general terms by Brooke (1954) in his monograph, while Lumb *et al.* (1955) reported a series of seven cases, and Roth *et al.* (1959) have drawn further attention to it. The term "toxic dilatation" was used by Marshak and his colleagues (1960), and this has the merit of drawing attention both to the extreme illness of the patient and to the fact that perforation of the colon is imminent.

During the last five years cases of chronic dilatation have been a source of special study in this centre, with particular regard to treatment. During this period 168 patients came to operation for ulcerative colitis; 14 had dilatation. It is our purpose to present the problems encountered in diagnosis, management, and the outcome. The following case reports are representative.

Illustrative Cases

Case 2

A woman secretary aged 41 was admitted in December, 1956, with a six-weeks history of diarrhoea with blood and mucus and a bowel frequency of D=5–6; N=1–2. She was pale and ill, with a deep venous thrombosis in the left leg; her abdomen was distended, the transverse colon being easily palpable, and there were exaggerated bowel sounds which were obstructive in character. The incomplete small-bowel obstruction was treated conservatively and settled. She was given hydrocortisone retention enemata in an attempt to control the colitis, but the abdominal distension increased and eventually a primary colectomy had to be undertaken.

Laboratory investigations showed: haemoglobin 13.1 g. per 100 ml. (88%); serum sodium 130, potassium 3.6, and chloride 95 mEq per litre; serum albumin 1.7 g. and globulin 2.5 g. per 100 ml.; blood urea 22 mg. per 100 ml. A straight radiograph of the abdomen showed marked gaseous distension of the bowel with fluid levels.

At operation the transverse colon was found to be adherent to the peritoneum, and was opened inadvertently in the abdominal incision. There was gross distension of the whole bowel, its wall being paper thin.

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Case 5

A farm manager aged 44 had a first attack of diarrhœa with blood and mucus one year before admission to hospital in January, 1957, with 12 motions in 24 hours, and this lasted six weeks. Nine months after the first attack he had an exacerbation, with a bowel frequency of 12–20 in 24 hours, which did not respond to medical treatment, and one month before admission he received cortisone in a dosage of 100 mg. a day. An initial response was not maintained and he deteriorated rapidly; barium enema examination in another hospital the day before admission showed a dilated colon with extensive pseudo-polyposis.

On admission he was extremely ill and grossly dehydrated, his limbs were wasted, and there was marked abdominal distension with a large dilated and easily palpable transverse colon. There was tenderness over the lower abdomen, with free fluid in the peritoneal cavity. He was passing only two or three motions a day. Pulse 120 per minute; temperature 102° F. (38.9° C.); blood-pressure 120/85 mm. Hg.

Laboratory investigations showed: Hb 7.8 g. per 100 ml.; P.C.V. 28%; serum sodium 122, potassium 4.6, and chloride 99 mEq per litre; serum albumin 2.8 g. and globulin 1.5 g. per 100 ml.; blood urea 19 mg. per 100 ml. A straight radiograph of the abdomen showed dilatation of the whole colon.

Because of the colonic dilatation and the fact that the patient had received large doses of cortisone it was feared that perforation was imminent, and strenuous resuscitative measures were therefore begun with a view to performing elective surgery as soon as possible. On the second day after admission his biochemical and haematological state had improved considerably with blood transfusion, but his general condition was slightly worse. The abdominal distension had increased, there was guarding and release tenderness over the lower abdomen, and there had been a definite increase in the free fluid within the abdomen; it was decided to proceed with an emergency primary colectomy with full corticoid "cover."

At operation the abdomen was seen to contain a considerable quantity of sero-sanious fluid and the mesentery was oedematous. The colon was intensely red and covered by a pannus of dilated blood-vessels. No overt perforation had occurred, but the whole of the transverse and descending colon was grossly distended, measuring some 12.5 cm. in diameter. The lateral wall of the descending colon was extremely thin and the lateral peritoneum was adherent to it, though complete dissolution of the bowel wall had not yet occurred.

Case 11

Six weeks before his admission in November, 1960, this patient, a 22-year-old industrial chemist, had developed diarrhœa which started as a looseness of stools, but later they contained blood and mucus, and he had been admitted to a regional hospital. There he had rapidly lost weight—3 stones (19 kg.) during six weeks. The frequency of stool was D=8–10; N=10–12 during the previous fortnight, except over the last 48 hours, when the frequency had become strikingly less, and on admission was only D=1–2; N=1–2. He had been treated with prednisone retention enemata over the last three days, and the diminished frequency of stool had been interpreted as a favourable response.

He was severely ill, mentally disorientated, and emaciated (see Fig. A), with pressure sores over the sacrum and ischial tuberosities, gross dehydration and anaemia, bilateral oedema of the legs, and peripheral abdominal distension. The dilated transverse colon could be clearly seen and palpated, and the bowel sounds were exaggerated centrally. There was some tenderness over the caecum and sigmoid colon, and his stools were composed entirely of blood and mucus. Pulse 120 per minute; temperature 101° F. (38.3° C.); blood-pressure 120/60 mm. Hg.

Laboratory investigations showed: Hb, 60%; P.C.V. 28%; serum sodium 122, potassium 4.2, and chloride 88 mEq per litre; serum bilirubin 0.6 mg. per 100 ml.; serum albumin 1.5 g. and globulin 2.8 g. per 100 ml.; blood urea 38 mg. per 100 ml. A straight radiograph of the abdomen revealed gross dilatation of the whole colon.

The patient was transfused with blood and his electrolyte deficiencies were corrected during the two days after his admission, and a primary colectomy was then undertaken.

At operation the whole colon was found to be grossly dilated and transformed into three large sacs—the caecum and ascending colon, the transverse colon, and the descending and sigmoid colons. The transverse colon was adherent to loops of jejunum and to the stomach. There was free fluid in the peritoneal cavity and the liver had a fatty appearance.

Case 12

Five months before his admission in March, 1960, the patient, a schoolboy aged 15, began to pass blood and mucus in his stools, with a bowel frequency of 2–3 in 24 hours which rapidly increased to D=25; N=10–20. He was treated with hydrocortisone retention enemata, and one month before admission a course of prednisone in a dosage of 5 mg. thrice daily was begun. Blood transfusion was required on four occasions, but one week before admission he became extremely weak and was unable to leave his bed. He had progressive loss of weight during the five months' duration of his illness.

He was a pale boy with a malar flush, emaciated and very ill; his abdomen was distended peripherally and was tender on palpation. The frequency of stool on admission was reduced to 3 in 12 hours, and the stools were composed almost completely of blood and pus. Pulse 140 per minute; temperature 103° F. (39.45° C.); blood-pressure 120/60 mm. Hg.

Table Summarizing Results in 14 Cases of Dilatation of Colon in Ulcerative Colitis

Case No.	Age and Sex	Duration of Disease	Duration of Distension (Days)	Potassium Level at Distension (mEq/litre)	Pre-operative Steroid Therapy	Perforation Found at Operation	Peritoneal Contamination during Operation	Results
1	53 M	1 month	4	4·5	+	+	++	Bowel found to be disintegrated at operation; died morning after operation
2	41 F	6 weeks	7	3·6	+	0	+	Died 17 hours post-operatively; aspirated vomit
3	36 F	1 year	1	3·6	0	0	0	Haemorrhage from rectal stump
4	19 F	7 months	7	4·0	+	0	+	Wound dehiscence
5	44 M	1 year	3	4·6	+	0	+	Wound and chest infection; septicaemia
6	23 M	2 months	7	3·9	+	0	0	Haemorrhage from rectal stump
7	51 M	14 ,,	6	6·0	+	+	+	Pre-operative tension pneumoperitoneum; died 5 days after operation from acute yellow atrophy of liver
8	23 M	2 years	8	4·6	+	+	+	Pre-operative tension pneumoperitoneum; no post-operative complications
9	47 M	23 years	5	5·1	+	+	+	Wound infection
10	68 M	20 ,,	7	4·3	+	0	+	Wound and chest infection; tracheotomy on 5th post-operative day; obstructive episodes; died 1 month after operation with terminal bronchopneumonia
11	22 M	6 weeks	3	4·2	+	0	+	Persistent pyrexia
12	15 M	3 months	2	5·3	+	0	0	No post-operative complications
13	37 F	10 years	3	4·6	+	0	0	Wound infecion
14	21 F	18 months	2	2·9	+	0	0	No post-operative complications

Laboratory investigations showed: Hb 6.3 g. per 100 ml.; P.C.V. 22%; serum sodium 126, potassium 5.3, and chloride 86 mEq per litre; serum bilirubin 0.3 mg. per 100 ml.; serum albumin 4.5 g. and globulin 5.7 g. per 100 ml.; blood urea 25 mg. per 100 ml.; prothrombin index 50%. A straight radiograph of the abdomen confirmed the colonic dilatation.

He was transfused with blood during the night following admission, and an emergency primary colectomy was performed in the morning with full corticoid "cover."

At operation he was seen to have considerable ascites, the bowel was diffusely involved, with a superficial pannus of vessels, and was strikingly dilated, in particular the transverse colon.

Results

Primary colectomy was performed on all 14 patients in this series who presented with dilatation of the colon; 10 survived (70%) and four died, among them the first two patients in the series (see Table). In Case 1 perforation of the colon had occurred before operation was undertaken, and gross peritoneal soiling was present; the patient died the following morning. At operation on Case 2 the transverse colon was found to be adherent to the peritoneum and was breached by the abdominal incision. This patient also died on the first post-operative day. The third patient who died (Case 7) presented with a dilated colon which had probably been perforated for six days, and he had developed a tension pneumoperitoneum. Primary colectomy was performed, but he died on the fifth post-operative day from acute yellow atrophy of the liver. The patient in Case 10 died one month after primary colectomy. Peritoneal contamination occurred during operation and a temporary obstruction developed during the post-operative period. In addition, emergency tracheostomy had to be performed five days after the colectomy; he eventually died following further obstructive episodes, with terminal bronchopneumonia. The remaining 10 patients survived and withstood operation well, often with dramatic resolution of pyrexia and tachycardia and rapid gain in weight. Post-operative complications included septicaemia (1), haemorrhage from the rectal stump (2), wound infection (3), and wound dehiscence (1).

Excision of the rectum has usually been deferred for two to three months as it has been found that to exceed this period is to invite technical difficulty because of the progressive gain in weight. Recently the interval between the two stages has been reduced further, so that rectal excision is carried out as soon as the patient has recovered from the first operation, often during the same hospital admission.

Discussion

In 5–10% of cases of ulcerative colitis severe colonic complications may be expected—perforation, pericolic abscess, diffuse peritonitis, massive haemorrhage, and carcinoma (Korelitz and Janowitz, 1960). It is only during the last decade that the further complication of a rapid and striking dilatation of the colon, associated with extreme intoxication of the patient, has been recognized as evidence of imminent perforation of the colon.

Several explanations of the cause of dilatation have been suggested. In a case described by Cohn *et al.* (1956) the patient showed signs of hypokalaemia, with a serum potassium level of 3.2 mEq per litre; restorative therapy with potassium led to recession of the mental deterioration, the small-intestinal hypomotility, and the colonic dilatation as the serum potassium level rose to 5 mEq per litre. Marshak *et al.* (1960), however, could find little evidence to support hypokalaemia as an aetiological factor. In only one of our cases (Case 14) was a serious depletion of potassium demonstrable biochemically, though all patients exhibited some degree of mental deterioration in spite of serum potassium levels within the normal range (see Table). It is more probable that these mental changes were attributable to the severe intoxication and debilitation of these patients rather than to a single biochemical factor. Bockus *et al.* (1958) have suggested that it is the destruction of the myenteric plexus that leads to the condition which they call "toxic aganglionic megacolon." Marshak *et al.* (1960), however, have pointed out that this term may lead to confusion with Hirschsprung's disease, where, of course, the aganglionic area lies beyond the megacolon, which is essentially normal bowel hypertrophied and dilated in response to chronic obstruction. These observations prompted us to re-examine the routine sections of dilated colons removed from four of our patients. The ganglion cells of Auerbach's myenteric plexus were present in all, and appeared histologically normal, suggesting the functional integrity of this system (Special Plate, Figs. 1, 2, and 3). The most probable cause of this condition is that the smooth-muscle cells are so damaged that they become impervious to their chemical environment. The extensive damage to the muscle cells leads to a loss of intestinal motility over such a length of the colon that the proximal bowel is physically unable to project its content through the paralysed segment. Reference to Special Plate, Figs. 1–6, demonstrates that the muscle fibres of the colon wall are pale and swollen and surrounded by inflammatory exudate to such a degree that normal functioning would seem to be unlikely.

As the disintegration of the large bowel progresses, the colon where it is in intimate contact with the parietal peritoneum becomes adherent to this, and as the erosion continues this latter structure becomes part of the bowel wall. This most commonly occurs in the sigmoid colon and less often in relation to the caecum. It is unusual to find this parietal adhesion of the transverse colon,

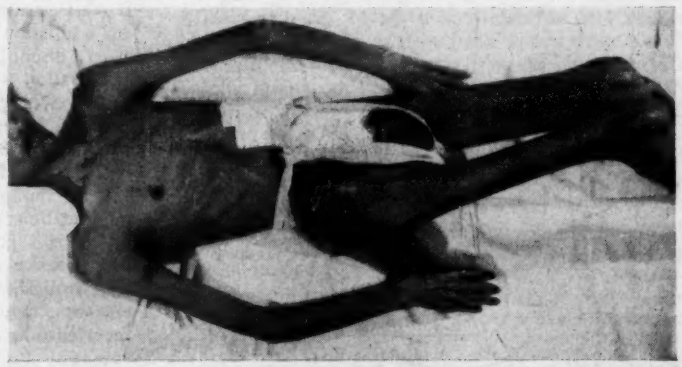

FIG. A.—Case 11. Patient on first post-operative day, showing severe emaciation.

though in rare instances loops of small bowel or omentum may come to perform a similar function. The colonic wall is so friable and soft that it is probably the mere weight of its fluid content and the tension of the contained gas which cause it to give way. The transverse colon is a dependent loop, and when disintegration is advanced it becomes a type of reservoir; further dilatation causes the splenic flexure to become more acutely angled, and in effect a valve develops, so that this combination of factors produces a form of retention with overflow (Fig. B).

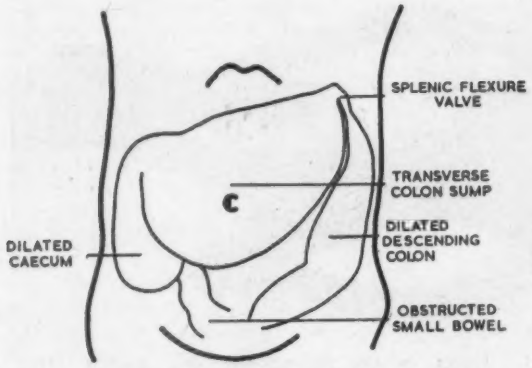

Fig. B.—Diagrammatic representation of dilatation of colon in ulcerative colitis.

Certain clinical features may render the diagnosis of colonic dilatation difficult. Brooke (1959) has drawn attention to the fact that in a comparatively short time the small bowel becomes affected *vis a tergo*, and a partial low small-intestinal obstruction occurs with its attendant symptoms and signs. The patient begins to vomit and experiences colic; exaggerated bowel sounds become audible, and central abdominal distension may progress to a stage where a ladder pattern supplements the distension of the transverse colon.

Similarly, in the course of dilatation of the colon and small intestine a further feature of great significance may appear which may also be misleading. Where the patient had previously had a marked frequency of motions the number becomes strikingly reduced as the distension advances. Instances have occurred (Cases 1 and 4) where this has progressed to a complete cessation of the passage of flatus or faeces and in which, at laparotomy, only a completely amotile, flabby, and disintegrating colon was found without any evidence of stricture or other mechanical obstruction (Brooke, 1959). In our experience this reduction in the frequency of stool has been liable to misinterpretation as either due to a mechanical obstruction (stricture or carcinoma) or even as a favourable response to the drug which was being currently prescribed. It is believed in this centre that if the diminution in the number of stools is not accompanied by improvement in the general condition of the patient operative intervention may be urgently indicated. Toxic dilatation of the colon can be diagnosed on sight if borne in mind; confirmation can then be made by a straight radiograph of the abdomen in the supine position, which demonstrates gaseous distension of the large bowel (Special Plate, Fig. 7), sometimes to a remarkable degree (Special Plate, Fig. 8). At this time it is almost impossible to decide whether perforation has occurred, since it may be clinically silent in this disease. Surgery should therefore not be delayed any longer than is necessary to correct dehydration and to restore, in part at least, the patient's electrolyte balance.

In all cases admitted to this centre fluid and salt depletions were corrected, and the patients transfused with blood to prepare them for operation, as rapidly as possible. It is the usual practice to provide full adrenal corticoid "cover" for those patients who have received corticoids systemically within the last three months if this treatment has been continued to the time of admission. If cortisone or its analogues have been discontinued no "cover" is provided, but preparation is made for the intravenous injection of 50 mg. of hydrocortisone during the operation if the blood-pressure undergoes a fall which cannot be accounted for by loss of blood. Where "cover" is provided the regimen has been as described by Slaney and Brooke (1957), though work is being carried out for the modification of this. Chloramphenicol is given for seven days post-operatively. Of the patients reported in this series, nine had received corticosteroids systemically, two had been treated with corticosteroid retention enemata, two with corticotrophin, and one patient had received no steroids at all.

Peskin and Davis (1960), reporting colonic dilatation in nine of 154 cases of ulcerative colitis, repeat the dictum of Ferguson and Stevens (1948) that these patients are too ill not to be operated upon, and they recommend colectomy. Marshak *et al.* (1960), however, practise a more conservative approach in the first instance, because of the risk of peritoneal contamination through bowel rupture, even if perforation has already occurred. They administer antibiotics and restore blood and electrolytes, and in addition intubate the small bowel. They are cautious in the use of adrenal corticosteroids, but are prepared to use them in the absence of perforation provided that the small bowel is decompressed by an indwelling tube, though it has been pointed out that this is seemingly an irrational step, since ileostomy always affords a more effective deflection of the faecal stream (*Lancet*, 1960).

There is a natural tendency to reduce operative intervention to a minimum, and to this end Marshak *et al.* (1960) have suggested caecostomy alone. When reporting results up to 1956 Brooke was inclined to the view that ileostomy alone might be less hazardous than primary colectomy in the really ill patient. However, technical difficulties as well as the need to remove the infected and ulcerated intestine impel primary colectomy for the following reasons. The manipulations necessary for ileostomy or caecostomy may rupture the fragile bowel. Peritoneal contamination is the greatest surgical hazard when the colon is removed for this condition, and yet ileostomy alone, as an emergency measure, does not remove the grave danger of perforation or haemorrhage, and often cannot be performed without damaging the colon. When such damage occurs the bowel wall is so friable that simple closure of the defect is difficult or impossible, and colectomy may become obligatory. Results in the present series, in which primary colectomy was undertaken on all 14 patients, appear to justify the policy of excision; ileostomy alone is inadequate, and caecostomy has even less to recommend it.

Summary

The clinical presentation of acute dilatation of the colon as a complication of ulcerative colitis is described. Four representative case histories from a series of 14 patients who presented in this way are reported.

It is suggested that neither hypokalaemia nor destruction of the myenteric plexus is an important aetiological factor in the development of this condition. A more likely explanation would appear to be that this condition is due to structural damage to smooth muscle by ulceration and inflammation advancing through the thickness of the intestinal wall.

The misleading clinical manifestations of small-intestinal obstruction and the significance of diminution of diarrhoea are discussed, emphasizing the pitfall of interpreting the latter as a favourable response to therapy.

The value of simple radiological examination of the abdomen, without recourse to barium studies, which would be dangerous in such circumstances, is also emphasized.

The policy of including colectomy in addition to faecal deflection in the treatment of acute dilatation of the colon in ulcerative colitis is justified by the results in this series.

We wish to thank Mr. Bryan Brooke, who operated on all 14 patients, for permission to publish details of cases under his care, and to acknowledge his guidance, encouragement, and advice in the publication of this paper. Our thanks are also due to the Department of Pathology and Mr. Dee of the Department of Clinical Photography, Queen Elizabeth Hospital, Birmingham, for the histological sections and photomicrographs.

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"We saw every variety of theoretical teaching. On the whole, the Doctors gave straight, informative lectures, very much, perhaps, in kind, if not in content, what they would give to their medical students. But there was a great difference between a quick, clear lecture delivered from the written text and ending with a perfunctory 'Any questions?', which were rarely, if ever, asked, and a more discursive, informal lecture with illustrations drawn from cases known to the Students and made lively by anecdotes and practical allusions. This kind of lecture might end with a battery of questions from the highly interested Students and a sharing with them of the Lecturer's ripe experience." (*Report on Pilot Investigation into Methods of Teaching in Nurse-Training Schools*, South-West Metropolitan Area Nurse-Training Committee.)

Preliminary Communications

Immunological Treatment of a Case of Choriocarcinoma

Increasing knowledge of the principles of homograft immunity has reawakened interest in the immunological status of the placenta and of its tumours (*Lancet*, 1958; Park, 1959; Bardawil and Toy, 1959).

Doniach *et al.* (1958) treated metastasizing placental choriocarcinoma in a woman by immunizing her with her husband's leucocytes, in the hope of activating specific homograft immunity against the tumour. Afterwards she showed an accelerated rejection of her husband's skin in a test graft and she had, at the time of the report, already survived longer than was then usual with this condition. Doniach and his colleagues made no strong claim for the treatment, which was complicated by other drug therapy, but thought that the homograft immunity may have acted against the tumour's supposed paternal component to retard its growth, and suggested that the same approach might usefully be tried by others who encountered this rare disease.

We report here that, in collaboration with members of the staff of the Queen Elizabeth Hospital, Adelaide, we have treated a case of choriocarcinoma in the same way. The patient died, and necropsy material was examined for evidence of an antitrophoblastic reaction.

Case History

A married woman aged 31 had two healthy female children aged 6 and 2 years. January, 1959: last menstrual period. May, 1959: vaginal bleeding. Curettings: hydatidiform mole with marked proliferation of the trophoblast. Hogben tests: positive June 8, negative June 12 and July 9, positive again in August and September. October, 1959: uterine haemorrhage, total hysterectomy and left ovariectomy. The uterus contained a polyp 2 cm. in diameter, section of which showed non-invasive viable trophoblast with no chorionic villi. Hogben tests: positive in December, 1959, and January, 1960. March, 1960: lung *x*-ray opacity, probably a tumour metastasis.

On admission to the Queen Elizabeth Hospital, Adelaide, in April, 1960, her principal complaint was backache and leg cramps, otherwise she was apparently in good health. She had no cough. Red and white blood counts were normal. *X*-ray examination showed no abnormality of the bony pelvis or spine; but there were multiple rounded opacities in both lungs.

Immunological Treatment and Tests

Blood samples were taken from the patient and from her husband, who came from unrelated families. The blood groups were:

	ABO	MN	P	Rh	Kell	Lewis	Duffy
Patient	AB	MN	P_1	CDe/CDe	Negative	Le(a–b+)	Fy(a+)
Husband	A	MN	P_1	cde/cde	Negative	Le(a–b+)	Fy(a–)

No serum antibody was detected in her serum when tested with her husband's cells in saline or albumin, or by the papain or antiglobulin techniques.

On April 14, 1960, a ten to fifteen times concentrate of the husband's leucocytes was made by dextran–citrate sedimentation of his blood and centrifugation of the

supernatant. The material was kept chilled, and within three hours of taking the blood 0.1 ml. of leucocyte concentrate was injected intradermally into each of the patient's arms and into her right thigh. No skin reaction or other anaphylactic symptom had occurred in one hour, and a further 0.5 ml. mixed with 0.1 ml. of Freund adjuvant was given intramuscularly in the left thigh.

Thereafter the husband was bled each week and a fresh leucocyte concentrate prepared, and the patient received a subcutaneous injection of 0.5 ml. without adjuvant in the upper part of each arm and each thigh weekly for 12 weeks, except for two occasions, at the ninth and tenth weeks, when one of the injections was given intravenously into the left cephalic vein. The longest delay between bleeding the husband and injecting the cells was six hours, the usual time being two to three hours. The leucocytes did not give rise to any immediate or delayed reactions, except that at the site of injection of the leucocyte-adjuvant mixture given at the start of the treatment a small fluctuant swelling appeared, and the patient said that several times this area became sore the day after her weekly subcutaneous injections, even though these were not close to it. (Eight weeks after the immunization treatment had finally been discontinued this small cold abscess caused by the adjuvant discharged a few millilitres of sterile pus and began to heal.)

Two weeks after the beginning of the immunizing course the radiologist reported that the opacities in the lungs had become much less prominent, and that there was no evidence of additional deposits. At the fourth week of immunization there was further *x*-ray evidence of improvement. So far the results were encouraging, but at the fifth week a Hogben test was still positive. At the seventh week complement-fixation tests on her serum, using saline extracts of human liver, kidney, thyroid, and lung extracts as antigens, were negative. At the eighth week the radiologist reported no significant change from the film of four weeks before. At the tenth week a test showed no serum antibodies (saline, albumin, papain, and Coombs techniques) active against the husband's red cells. At the twelfth week new *x*-ray shadows appeared in both lungs.

Throughout the course of immunization the patient's leucocytes were regularly counted and their numbers remained steady and within normal limits. There was no noteworthy increase in the absolute number of lymphocytes, nor did any abnormal mononuclear cells or plasma cells appear in the blood films. Subjectively, she developed some personality changes of a mildly obsessive type, and complained from time to time of pains in the lower limbs and pelvis for which no cause could be found.

Intradermal skin tests were carried out a week after the end of the immunization treatment, using 0.1 ml. of (*a*) leucocyte suspensions, (*b*) erythrocyte suspensions, and (*c*) cell-free plasma–dextran mixtures obtained (1) from the patient herself, (2) from her husband, and (3) from an independent donor—that is, nine tests in all. The only reaction was a small immediate weal (0.5 cm. in diameter) which appeared at the site of injection of the husband's leucocytes and faded in two hours. The test sites were observed for 36 hours and there was no further reaction. (It had been thought that satisfactory immunity in the patient might have been indicated by a delayed type of reaction to the husband's leucocytes.)

Skin grafting was then performed. Three full-thickness grafts (2.5 cm. square) were made to the patient's right forearm: (1) an autograft from her own thigh, (2) a homograft from her husband, and (3) a homograft from an independent female donor (not the same individual who contributed the control leucocytes for the skin test) whose blood group was:

ABO	MN	P	Rh	Kell	Lewis	Duffy
A	M	P_1	CDe cDE (probable)	Negative	Le (a–b+)	Fy (a–)

All grafts took. The husband's skin was rejected on the eighth day and that of the independent donor on the twenty-eighth day, while the patient's autograft survived. Satisfactory homograft immunity towards the husband's tissues was therefore presumed to be present, and ought to have been even further enhanced by the grafting.

At this time treatment with 6-mercaptopurine was begun: 120 mg./day was given for 15 days and then 300 mg./day for 10 days. This produced some anaemia and granulocytopenia (but not lymphopenia), with fever, sore throat, mouth ulcers, and perionychiae. These subsided after treatment with tetracycline and a number of uneventful blood transfusions, and her leucocyte count quickly returned to normal. The radiologist reported considerable clearing of the shadows in both lungs, but the Hogben test remained positive. For two weeks she felt comparatively well, and left hospital. She was readmitted on September 19 suffering from sudden haemoptysis and shock. Radiography revealed the reappearance of very extensive lung metastases. She became increasingly cyanotic and died on September 29.

A complement-fixation test was carried out, using her serum taken in the last week of her life, with saline extracts of the tumour and of macroscopically normal lung obtained at the subsequent necropsy as antigens. No complement was fixed, and parallel tests, using saline extracts of human kidney, liver, lung, thyroid, and placenta, from other sources, were also negative, as was a last check for anti-erythrocyte antibodies active against her husband's blood by the saline, albumin, papain, and Coombs techniques. The antistreptolysin-O titre was 1/320. (A titre of this level usually indicates a recent response to a streptococcal infection. This probably occurred when she had the pyrexia, sore throat, stomatitis, and perionychiae which had responded to tetracycline treatment four to six weeks before death, but the lesions were not examined bacteriologically at the time.) The paper electrophoretic pattern of this same serum sample showed a normal level of gamma-globulins (1.06 g./100 ml.), beta-globulins, and alpha$_2$-globulins, with raised alpha$_1$-globulins and lowered albumin (Fig. 1).

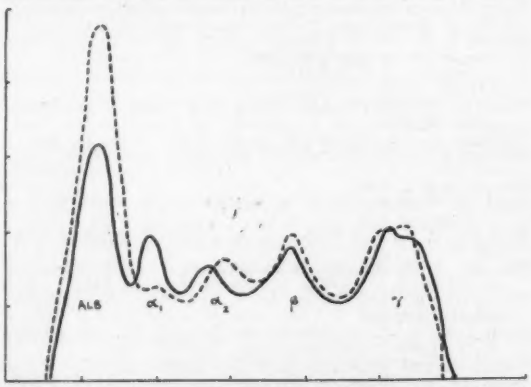

FIG. 1.—Scanned paper electrophoretic pattern of the patient's serum in the last week of her life. Continuous line: patient. Broken line: normal control serum.

NECROPSY

Multiple haemorrhagic rounded deposits of tumour were seen throughout the lungs at necropsy, performed by Dr. Meadows. There was an isolated single deposit in the right adrenal gland, and others were in the white matter of the brain. No tumour was found in the liver or kidneys. The right ovary contained a haemorrhagic luteal cyst. Histological examination showed that the tumour was a choriocarcinoma, and that the lungs were very widely infiltrated, even apart from the obvious macroscopic sites. Cytotrophoblast and syncytial trophoblast could be identified. Dr. Meadows kindly provided us with material for study, and also lent us some of his own sections.

The tumour had a bland relationship with the adjacent normal tissues which it was invading. No lymphocytic, plasma cell, macrophage, or eosinophil infiltration, such as would have indicated a cellular or immunological reaction against the tumour by the patient, could be seen in direct association with its margins when these were in clear-cut contact with maternal tissues, uncomplicated by haematoma (Fig. 2). Certain of the larger deposits had undergone central necrosis, but such areas again were not the focus of any inflammatory cell infiltration.

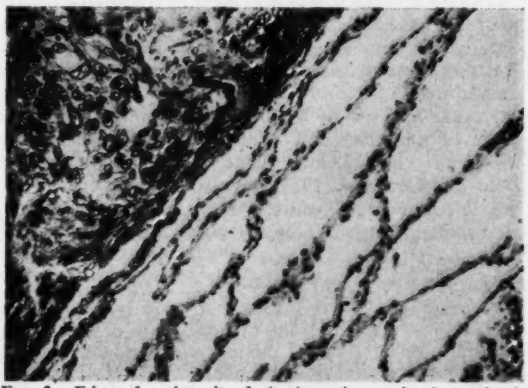

FIG. 2.—Edge of a deposit of choriocarcinoma in the patient's lung, showing absence of inflammatory reaction. (Section kindly lent by Dr. Meadows.)

There were some spaces containing free blood within the tumour masses. It was not possible to see whether these were invariably lined with syncytial trophoblast—that is, whether they were the circulatory equivalents of placental intervillous blood spaces. However, the maternal blood within them contained the normal proportions of polymorphonuclear leucocytes and lymphocytes and they evidently formed the more intimate blood supply of the tumour. Yet again there was no sign of any leucocyte infiltration proceeding from these points.

Many of the air spaces of the adjacent lung contained blood clot, which at different sites was seen in various stages of resolution or organization. This free blood in the alveoli had provoked the usual cellular reaction: an intra-alveolar exudate of polymorphonuclear leucocytes with a few lymphocytes and fibroblasts and many haemosiderin-laden macrophages. It seemed likely that it was the resolution of these haematomata associated with many of the tumour deposits which gave the *x*-ray appearances suggesting regression of metastases during the earlier stages of the disease when immunization was being carried out.

Sections taken from the site of injection of the leucocyte-adjuvant mixture in the left thigh showed a healing granuloma of conventional lipoid-tuberculoid type with fibroblasts, epithelioid cells, lipoid-laden macrophages, giant cells, plasma cells, and aggregations of lymphocytes.

Sexing the cytotrophoblast of one of the deposits by the method of Park (1957) gave a sex-chromatin incidence of 3%. Adjacent smooth muscle cells and fibroblasts of the patient's bronchi were clearly female with an incidence of 65%. Sexing trophoblastic tumours is probably, as Park's paper indicates, not entirely reliable, but it is a reasonable presumption that the tumour in this case was male. (The sections of the hydatidiform mole of May, 1959, were re-examined but its state of fixation was not good enough for sexing.)

DISCUSSION

The main argument against attempting active immune treatment of choriocarcinoma is that the tumour itself ought surely to be an abundant antigenic stimulus, and if the patient was going to respond at all, no further boosting by injections should be needed. But the phenomena of immunity are not easy to predict in novel situations. For instance, variations in antigenic potency, hapten formation, differences in penetrability of cell-borne and serum antibodies and antigens through living membranes, lack of uniformity of response to antigens administered by different routes or in different media or to different species, are all well known and might be relevant in these particular circumstances. It is just possible that adult leucocytes, sharing antigens with the placenta but having them in more complete or more available form, could stimulate homograft immunity against placental tissue which was itself antigenically ineffective in the body.

Embryonic tissues are known to be less antigenic than those of the adult, but whether reduced antigenicity of this kind would be partial or total in the placenta is open to conjecture. The human foetus certainly contains some antigens which can stimulate an immune response in the mother before a pregnancy is over, as in erythroblastosis foetalis, so perhaps a very prolonged antigenic stimulus by trophoblastic tissue might sometimes lead to an antitrophoblastic immunity. There could indeed be a range of de-differentiation to be found in various trophoblastic tumours, some losing all their markers or antigens and thus being able to grow without stimulating any immune response on the part of the host, and others eventually provoking a reaction by which they are rejected. This could explain the occasional well-documented cases where a spreading choriocarcinoma has completely regressed, and it would be interesting to test the reactions of such fortunate patients to comparative grafting with their husband's and others' skins.

A cellular response is the histological sign of incipient homograft rejection, or indeed of any immunological reaction *in vivo*. If a tumour were the target of such a reaction one would expect to find lymphocytes, plasma cells, and perhaps macrophages and eosinophil polymorphonuclears in its immediate vicinity. If it were surrounded by a protective layer impermeable to these cells, perhaps it could survive in spite of their presence. If it were being destroyed by them there should be evidence in some histological sections that they were infiltrating it.

Park (1958) studied experimental trophoblastic embolism in mice and noted that the effect of the placental particles in the lungs was that of unusually bland emboli, exciting little or no inflammatory response. In contrast, Ober (1959) has published details of a human case of widespread trophoblastic embolization of the pulmonary artery where the walls of some of the vessels harbouring the emboli were diffusely infiltrated by inflammatory cells.

In the case we report here there was good biological evidence of homograft immunity having been developed towards the husband's skin. In spite of this there was no histological sign in the necropsy specimens of a general cellular reaction at the margins of the tumour or of an infiltration of its stroma or of its necrotic parts. This suggests either that it had lost or never shared homograft antigens with the husband's skin or that the patient's capacity to produce the right kind of immune response was in some way weakened. Something of the nature of immunological paralysis or unresponsiveness may have been at work, but we have noted that she was capable up to the end of her life of producing normal scavenging and granulomatous cellular reactions to

autogeneous blood clot in the lung alveoli, and to a foreign irritant in the adjuvant site. Her blood lymphocytes were not reduced in quantity. She had recently developed high-titre antistreptolysin-O serum antibodies, and her serum globulins were not below the normal level. She had rejected two skin homografts. All this argues that her general capacity for immune responses was not impaired.

The normal placenta is not rejected as a homograft. On the whole, we conclude from the evidence here that this choriocarcinoma was also effectively non-antigenic. The simplest explanation is that its trophoblast was exhibiting the same mechanisms or properties of physiological non-antigenicity (whatever they may be) that exist in the normal placenta.

SUMMARY

A patient with placental choriocarcinoma was treated by immunization with her husband's leucocytes, and subsequent homograft immunity against his skin was demonstrated.

In spite of this, the tumour did not regress and the patient died.

Examination of serum and of necropsy material indicated that the patient had normal immune responses, but no serological or histological evidence of an antitrophoblastic effect was found.

Many specialists made their records, opinions, techniques, and materials freely available to us in connexion with this case. We are grateful to Dr. Thatcher and Professor Cox (clinical management), Dr. Hardy (biopsy reports), Dr. Meadows (necropsy notes and specimens), Dr. Brendish (antistreptolysin-O titration), Mr. Opit (skin grafting), Dr. Jones (*x*-ray reports), Dr. Lewis (blood grouping), and Dr. Roman (electrophoresis).

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Anticoagulant Therapy in Superior Mediastinal Obstruction

[WITH SPECIAL PLATE]

Superior mediastinal obstruction occurs in patients with carcinoma of the lung and may occur in association with metastases from other carcinomata, such as of the breast, and in the reticuloses (McIntire and Sykes, 1949). In patients with carcinoma of the lung the obstruction is often relieved by a course of radiotherapy; however, 20–30% of such cases fail to respond and 20% recur after adequate treatment (Szur and Bromley, 1956).

In carcinoma of the lung the obstruction is due to enlarged superior mediastinal lymph nodes compressing the main veins or to direct infiltration of the veins by tumour tissue. Thrombosis of the veins may be associated with the obstruction, and in Szur and Bromley's series was present in 8 of 23 cases in which necropsy was performed. Localized phlebitis with thrombus formation, but without the presence of neoplasm, can also produce superior mediastinal obstruction (Ochsner and Dixon, 1936).

Since patients with mediastinal obstruction failing to respond to radiotherapy will die rapidly, other forms of treatment should be considered. One such method—namely, anticoagulant therapy—could be of value in relieving the obstruction by allowing recanalization of the thrombosed veins, or in aiding the development of a collateral circulation; this method has been used in the seven cases described below. Phlebography was carried out in three of these cases in an attempt to find the cause and site of the obstruction and to assess the value of the treatment. The phlebograms all showed thrombosis in the innominate and subclavian veins. Veal and Cotsonas (1952) have shown that these veins are as commonly affected in the syndrome of superior mediastinal obstruction as the superior vena cava itself.

CASE 1

A man aged 49 was found in January, 1960, at a thoracotomy performed by Mr. G. Flavell, to have an inoperable undifferentiated carcinoma of the lung involving the mediastinum and superior vena cava. He was given a course of radiotherapy to the mediastinum in March, 1960. In July he was admitted to the London Hospital with a history of sudden swelling of the face and arms, blueness of the lips, and increasing dyspnoea, all maximal in 24 hours. Examination showed gross oedema of the face, neck, and arms down to the fingers. He had cyanosis of the lips and orthopnoea, and needed oxygen every 15 minutes to relieve his discomfort. There were only a few collateral veins in the chest wall. A chest radiograph showed some fluid at the right base, but no sign of mediastinal widening. A phlebogram disclosed a complete block of both subclavian veins and upper superior vena cava, with some collateral circulation (Special Plate, Fig. 1).

Anticoagulant therapy was started with intravenous heparin and continued with "dindevan" (phenindione). Within two weeks the symptoms and signs of obstruction had very much improved, and he was discharged with his prothrombin index stabilized at 50% and taking 200 mg. of dindevan daily. A month after starting the course of anticoagulants he was readmitted. There were no symptoms of mediastinal obstruction, apart from slight oedema of the neck. Phlebography was again carried out, and this showed that the superior vena cava and subclavian veins were still blocked but that there had been a considerable increase in the collateral circulation, particularly through the intercostal veins (Special Plate, Fig. 2). He was discharged from hospital and continued to taken dindevan, but by the end of September his general condition began to deteriorate and his liver was involved with neoplasm. He finally died in November, 1960, but with no return of the superior mediastinal obstruction.

CASE 2

A man aged 45 had a thoracotomy in March, 1960, when an inoperable carcinoma of the left lung was found. In June, 1960, he was treated with radiotherapy for lymph-node metastasis in the neck. The nodes became smaller, but he became increasingly breathless, and in August was found to have mediastinal obstruction as evidenced by the swelling of face and arms, raised jugular venous pressure, cyanosis, orthopnoea, and distended collateral veins in the chest wall. A chest radiograph showed opacity of the left upper chest, with the mediastinum deviated to the right. A course of radiotherapy to the mediastinum was started using a pair of parallel opposed fields of 15 × 10 cm., giving a tumour dose of 3,750 rads in 15 days, but with no relief of the

obstruction. A phlebogram taken at this time showed complete blockage of the left innominate vein, but a normal right innominate vein and superior vena cava (Special Plate, Fig. 3).

In September anticoagulant therapy was begun with intravenous heparin and continued with dindevan, and a week later the swelling of the face and arms and the orthopnoea became less. He was discharged when his prothrombin index became stabilized between 35% and 37%, and continued on dindevan 100 mg. daily as an out-patient, attending weekly for prothrombin-time estimation.

In November there were no symptoms or signs of superior mediastinal obstruction, though lymph nodes in the left supraclavicular fossa were still swollen, the largest 2 cm. in diameter. A phlebogram performed at this time showed some recanalization of the left innominate vein and decrease of the collateral circulation (Special Plate, Fig. 4). When last seen in February, 1961, there were no changes in the signs or symptoms.

CASE 3

A woman aged 58 had a left simple mastectomy performed by Mr. J. E. Richardson in January, 1958, for a carcinoma of the breast, and this was followed by a course of radiotherapy. In June, 1960, superior mediastinal obstruction developed, and she was given radiotherapy to a tumour dose of 2,500 r in 13 days with a good response. However, in September she complained of sudden swelling of the face and left arm and extreme dyspnoea, which reached its maximum in two days. On examination she was found to have all the signs of superior mediastinal obstruction with enlarged lymph nodes in the neck, but a chest radiograph showed no evidence of mediastinal enlargement. A phlebogram revealed occlusion of the left subclavian and innominate veins (Special Plate, Fig. 5). A course of anticoagulant therapy was begun, and within a week the breathing became easier and the left arm less swollen. When her prothrombin index was stabilized at 37% she was discharged; she took 50 mg. of dindevan twice daily and was seen at weekly intervals as an out-patient. A month later, in December, 1960, she was readmitted because of further enlargement of the lymph nodes in the neck and the presence of cutaneous metastases on the chest wall. The mediastinal obstruction was no worse, and in January, 1961, a phlebogram showed little change.

CASE 4

A man aged 70 was given a course of radiotherapy for an inoperable carcinoma of the lung in March, 1957. This treatment was repeated in November, 1958, for recurrent tumour in the lung.

In January, 1959, signs of superior mediastinal obstruction developed, with dyspnoea, oedema of the face and right arm, and dilated neck veins. This was treated with *x* rays, using a pair of parallel opposed 15 × 15 cm. fields to the right upper chest and mediastinum giving a tumour dose of 2,500 r in 20 days. The swelling of the face and neck lessened after a few days' treatment, but then rapidly became worse than before. He was readmitted in February, 1959, and a course of anticoagulant therapy was started. Three weeks later he was discharged with definite improvement in the mediastinal obstruction. The prothrombin index was stabilized at 65%, and he continued to take dindevan, 50 mg. twice daily, as an out-patient. However, his general condition deteriorated, and he died in the following April.

CASE 5

In June, 1960, a woman aged 50 complained of aching in the neck and loss of weight. In July she noticed swelling of the face and neck and shortness of breath on exertion. She was admitted to the London Hospital on August 15 under the care of Dr. N. L. Rusby as an emergency on account of rapidly increasing dyspnoea. On examination she was found to have puffiness of the face, neck, and upper arms, dilated veins on the chest wall, fixed distension of both external jugular veins, and marked orthopnoea. Soft nodes were palpable in both sides of the neck, the axillae, and groins. Investigations showed a haemoglobin level of 80%, with 9,600 leucocytes per c.mm. and a normal differential count. A chest radiograph showed a shadow in the right upper lobe, minimal widening of the right superior mediastinal shadow, and a small right pleural effusion. The sputum was repeatedly positive for malignant cells. A diagnosis of carcinoma of the lung with superior mediastinal obstruction was made and a course of radiotherapy to the mediastinum started. There was slight improvement after the first day's treatment, but by the end of the course of treatment (15 × 15 cm. parallel opposed fields giving a tumour dose of 3,000 r in 13 days at 220 kV) the signs of obstruction suddenly became worse overnight with increased oedema of the left arm and left side of the neck. A course of anticoagulant therapy was therefore started, with dramatic improvement in the mediastinal obstruction, and even after only three days on this treatment there was some reduction in the facial swelling.

Unfortunately, the neoplastic process spread to the abdomen, causing distension and discomfort. She had a small haemoptysis at this time. She was discharged from hospital on October 13 with no signs of mediastinal obstruction, and continued to take dindevan, 50 mg. twice daily, as an out-patient. The prothrombin index was stabilized at 40–45%.

Her general condition continued to deteriorate, and she died on November 7, but without further evidence of mediastinal obstruction.

CASE 6

A man aged 60 was given a course of radiotherapy for carcinoma of the lung (2,500 r tumour dose in two weeks) in June, 1960. There was symptomatic improvement, but in September he suddenly developed signs of mediastinal obstruction. In view of the recent irradiation therapy, which had produced no radiological improvement, a course of anticoagulant therapy was started. As no relief of symptoms followed this treatment he was given nitrogen mustard intravenously to a total dose of 35 mg., but still with no effect. His condition deteriorated, and he died in November, 1960.

CASE 7

A man aged 61 was given a course of radiotherapy in January, 1960, for superior mediastinal obstruction due to carcinoma of the lung. He rapidly became symptom-free, remaining well for six months. In September, 1960, there was a sudden onset of breathlessness and swelling of the face and neck, maximal in a few hours. At this time he was found to have gross signs of mediastinal obstruction and a right pleural effusion, and a chest radiograph showed complete opacity of the right lung field. A palliative course of radiotherapy was started, but as there was no improvement after a week's treatment anticoagulant therapy was begun. Radiotherapy was continued up to a total dose of 2,500 r in 14 days at 250 kV; the anticoagulant therapy was also continued, but with no effect, and he died at the end of October, 1960.

DISCUSSION

The classic symptoms and signs of superior mediastinal obstruction—namely, swelling of the face, neck, and arms, orthopnoea, cyanosis, raised jugular venous pressure, and collateral veins on the chest wall—usually develop slowly, often taking a few weeks to reach their maximum intensity. In the cases above described the symptoms were sudden in onset and the signs maximal within one to three days, suggesting a fairly sudden blockage of the venous return to the heart, such as would occur in thrombosis of the main mediastinal veins.

In the majority of cases of superior mediastinal obstruction the chest radiograph shows evidence of a tumour in the superior mediastinum, even when the primary tumour is not obvious (Roswit *et al.*, 1953). In two of our cases (Nos. 3 and 5) there was no such *x*-ray evidence, though Case 3 did have an enlarged mediastinal shadow four months previously when under treatment with *x* rays. If thrombosis were the main cause of the mediastinal obstruction, *x*-ray changes would not necessarily be present; in these cases phlebography may be of help in establishing the diagnosis (Roswit *et al.*, 1953), and this is well shown in Case 3.

In the U.S.A. phlebography has been widely employed in the investigation of superior mediastinal obstruction (Katz *et al.*, 1947; McIntire and Sykes, 1949; Hudson, 1957) and in the investigation of vessel involvement in carcinoma of the lung (Steinberg and Finby, 1959). In Great Britain, however, the use of phlebography in obstruction of the veins of the superior vena caval system appears to have received little attention. Injection of contrast medium by hand through a needle or cannula introduced percutaneously into an antecubital vein tends to yield results of uncertain quality. Injection through a jugular catheter would appear attractive when it is certain that the superior vena cava and proximal innominate veins alone are involved. Thromboses, however, tend to involve more peripheral vessels.

In this investigation phlebography was performed in Cases 1, 2, and 3 by introducing radio-opaque catheters into veins of both antecubital fossae and passing them, if possible, as far as the axillary veins under screen control. Injection of about 50 ml. of 45% "hypaque" (sodium diatrizoate) at a pressure of 50 lb. per sq. in. (3.5 kg. per sq. cm.) through a split output was made with a Talley pressure injector. Films were taken at intervals either manually using a Garrow box or with an "elema" A.O.T. film-changer.

The anatomy of superior vena caval obstruction and its collateral circulation has been previously described. The description of McIntire and Sykes (1949) of the phlebographic findings, incorporating the earlier experimental work of Carlson (1934), has not been significantly changed by later workers.

Treatment by radiotherapy for superior mediastinal obstruction is well recognized, and is usually successful when a minimum tumour dose of 3,000 r in three weeks is given (Bignall, 1958). Response to such treatment is very rapid, and even after the first few days some alleviation of the patient's condition becomes apparent, and in all cases some relief will have occurred by the end of treatment.

When no treatment at all is given to patients with superior mediastinal obstruction due to carcinoma the average survival time will be less than 10 weeks, the majority of patients dying in less than four weeks from the onset of symptoms (Roswit *et al.*, 1953). Of the seven cases in this series, five showed relief of symptoms for periods ranging from two to six months, the average survival time being four months.

We have used anticoagulant therapy only in cases in which there was clinical evidence of thrombosis and which have failed to respond to radiotherapy or were considered unlikely to do so. Treatment has been with intravenous heparin followed by oral anticoagulant (dindevan) therapy. When the prothrombin index has become stabilized between 35 and 65% patients have been discharged to attend a follow-up clinic weekly, the prothrombin index being estimated at each attendance. The one complication which we expected to occur—haemorrhage from an ulcerated tumour of the bronchus—was obvious in only one case, and caused no more than a slight increase in the haemoptysis which had already been present for some time.

It is suggested that anticoagulant therapy be considered in cases failing to respond to radiotherapy, or in cases in which, having once been successfully treated by radiotherapy, mediastinal obstruction subsequently redevelops with clinical evidence of thrombosis of the main veins. It is possible that the over-all results of treatment of superior mediastinal obstruction might be improved if a combination of radiotherapy and anticoagulant therapy were to be tried.

We wish to thank Dr. J. A. Orr for his help in preparing the paper; and Dr. N. L. Rusby, Mr. G. Flavell, Mr. J. E. Richardson, and Dr. W. Shanks for permission to publish their cases.

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Medical Memoranda

A Case of Localized Cervical Disk-arthrosis

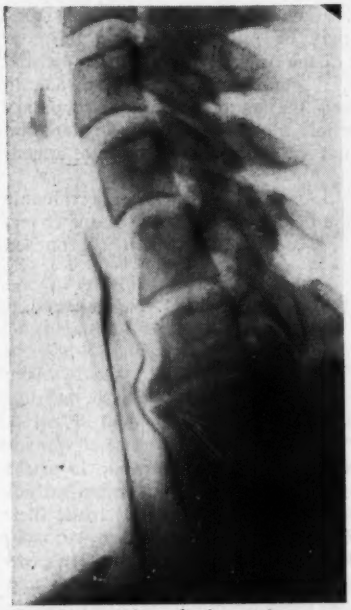
The subjective troubles and the objective clinical picture that may result from cervical spondylosis can be very different. A syndrome in which the symptoms complained of and the signs observed are in exact accord is less frequently met with, and we describe a case of this type here.

CASE REPORT

A housewife aged 42 had had her tonsils removed in 1955. She suffered from chronic adnexitis. For some time she had felt pain in both hips and recently in the neck also. Her main complaint, however, was that for six years she had a slight feeling of oppression in the throat, a little below the larynx, when she swallowed. She said it was as if food stuck at this point, passing on through the oesophagus only when it had overcome some impediment. She was often forced to cough, and when swallowing larger pieces of food she had slight difficulty in breathing. There were no other complaints. Various possibilities were considered in the course of the past six years: cancer of the larynx, a retrosternal goitre, a mediastinal tumour, and even globus

hystericus. After detailed examination in a general hospital, the results of which were negative, she was referred to our institute.

The patient was afebrile, of good physique, and well nourished; there were no signs of wasting. Her general condition was normal. Arterial blood-pressure was 120/80 mm. Hg and pulse 72. There was slight emphysema of the lungs. The heart was normal, as was the thyroid gland. The B.M.R. was +5%. The neurological condition of the cervical and brachial plexus was normal. E.S.R. 10 mm. in one hour. The blood picture and the results of urine examination were normal.



Oesophagography of the patient presented. Impression of the posterior wall of the oesophagus by ventral osteophytes, causing a marginal defect in filling exactly at the site of discomfort indicated by the arrow.

So far as evidence of rheumatic changes was concerned the mobility of both hips was slightly limited and painful, and radiographs showed early coxarthrosis. There were moderate crepitations in both shoulders. The lower part of the cervical spine was tender on movement. *X*-ray examination showed narrowing of the disk C 6–7 with thorn-like osteophytes at the front edge of the vertebral bodies, projecting forward, with a tendency to form an osseous connexion. When the patient swallowed contrast medium in the course of oesophagography it was seen that the posterior wall of the oesophagus was distinctly pressed in at that point, and there was a marginal defect in filling at the level described. The configuration of the oesophagus in all other parts was regular and smooth (see Fig.). During the swallowing of the contrast medium the patient indicated that the site of the discomfort was exactly at the level of the local diskarthrosis described.

DISCUSSION

The first description of vertebral osteophytes pressing on the oesophagus was probably given by Zahn (1905, 1906). Hall and Osborne (1958) described such a case with a massive osteophyte at the level T 8–9 but without trouble in swallowing. They mention that such massive osteophytes are often encountered on the lower part of the cervical spine, but seldom on the lowest segments. From our experience with a large number of cases, massive ventral osteophytes on the lower cervical spine are not uncommon, but they seldom cause difficulty in swallowing.

Disturbances of swallowing connected with cervical spondylosis can be caused either mechanically, as in the above case, or by the passing over of degenerative inflammatory periarticular processes to the prevertebral connective tissue. In addition, the disturbances may arise in a spastic-reflectory way or because of psychogenic factors (Schröer, 1959).

The cases most often met with in our practice are those in which, besides a cervical spondylosis, there occurs an irritation either of the cervico-brachial nervous plexus, in the sense of a "cervical syndrome," or of the sympathetic system (Isemein and Ramis, 1957), when it is known that various clinical features may arise, such as dizziness (Ryan and Cope, 1955), headache (Hercog, 1949), precordial pain (Stanojević, 1957), many other visceral functional disturbances, anginous attacks, and digestive troubles. Disturbances of swallowing are less often encountered, and when they occur are often of functional origin, for such a massive osteophytosis is not found on the spine. On the other hand, we have observed a series of cases with distinct ventral osteophytosis—not so marked, however, as in the above case, and with the osteophytes directed more steeply downwards—without disturbance of swallowing, but with evident signs of irritation of sensory, motor, and/or vegetative nervous elements.

In the above case there existed a massive localized change in the sense of disk-arthrosis, without marked spondylous changes in other parts of the cervical spine, except for a diminished lordosis. On oesophagography the change described corresponded exactly to the site of the functional disturbance indicated by the patient. The difficulty in swallowing—a distinct visceral symptom—was caused by direct pressure on the posterior wall of the oesophagus.

From the therapeutic point of view such cases are unrewarding. In the opinion of most authors, treatment should be conservative. We applied local *x*-ray therapy, which temporarily was almost entirely effective.

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"There is a general impression that the investigation and control of trade waste discharges to the sewers of London only started when the 1953 General Powers Bill became law. This is certainly not true, for the writer and his colleagues in the branch still have vivid recollections of walking through sewers for the first time to examine damage to brickwork and jointings, although it is thirty years ago. Also, it was most interesting to discover recently among the laboratory records a laboratory notebook of the chemical department of the Metropolitan Board of Works—the predecessor of the London County Council. The book, a vellum-bound volume with entries written in a beautiful copper-plate hand, is dated January, 1881, to January, 1884. Amongst a variety of investigations are found analyses in connexion with 'the Thames pollution Enquiry' and analyses of 'Cow Shed' waters which were, in the main, generously polluted by cesspit drainage. The anonymous analyst's usual comment was, 'Not fit for potable purposes,' but one sample merited the comment, 'This is the most disgusting sample I have ever smelt.'" (*Annual Report of the Scientific Adviser for the Year 1960*, London County Council Public Health Department—Scientific Branch.)

Reviews

HANDICAPPED CHILDREN

Handicapped Children. By John D. Kershaw, M.D., B.S., M.R.C.S., D.P.H. (Pp. 228+x. 21s.) London: William Heinemann. 1961.

This is an excellent book, well written, delightful to read, and full of wisdom. Handicapped children present problems in many ways and to many different people, not least to themselves. The author's personal experience in dealing with such children has given him the opportunity of reviewing the problems encountered and the best methods of forestalling or counteracting them. He stresses the importance of forecasting the future circumstances in which affected children's lives will have to be planned and the need for assessing function rather than anatomy in this planning.

Encouragement for those whose work is with physically handicapped children is given by reminding them that these children may receive compensation for their disability by developing their powers of concentration of effort and purpose to a greater degree than that achieved by many normal people, and that they may indeed grow up to appreciate their physical handicap as a personal challenge. The need for constantly remembering this positive aspect of compensation is one of the author's main themes.

In the various chapters he considers the reactions of people in general and of parents in particular to "abnormal" children and the problems of training for work, recreation, and educational assessment. Blindness, deafness, and epilepsy are admirably discussed, and there are excellent chapters on physical and mental subnormality, cerebral palsy, delicate children, the maladjusted, and the child with multiple handicaps. Finally there are two appendixes, one on the position and problems of handicapped children in less developed countries and the other on legislation in Britain for the protection and help of handicapped children.

This book gives such wise advice and encouragement that it should be read not only by doctors but by all who have to care for the handicapped, and it is a tribute to the author that it is so written that it may be understood and enjoyed equally by the non-qualified workers in this field.

WILFRID GAISFORD.

BIBLIOGRAPHY OF DIABETES

Index zum Diabetes Mellitus. Eine Internationale Bibliographie. By Professor Dr. med. et phil. Joseph Schumacher. (Pp. 878+xlviii. DM. 286. Munich and Berlin: Urban and Schwarzenberg. 1961.

Dr. Joseph Schumacher, director of the Institute of Medical History of the University of Freiburg, has undertaken an enormous task in compiling this bibliography of diabetes. The preface and explanations are given in English, French, and German. A brief historical review of the subject (in German) follows. The main body of the bibliography lists well over 20,000 references and this is followed by an index of authors.

The papers listed are grouped into subjects. To ascertain what has been written on any particular topic the appropriate heading must be consulted. These cover both general subjects and many specialized clinical, aetiological, and therapeutic aspects. Some of the sections are very long and this makes reference difficult—for example, there are 50 pages on all aspects of insulin therapy. It is much simpler to trace the writings of any particular worker through the index of authors.

The references have been compiled mainly from such publications as the *Index Medicus* and the *Quarterly Cumulative Index*. The author admits that some important papers may be missed by doing this. A striking omission is of the original paper by Kimmelstiel and Wilson (*Amer. J. Path.*, 1936, vol. 12, p. 83), in which they described the characteristic intercapillary lesions of the renal glomerulus, the explanation presumably being that the word diabetes did not appear in the title.

There can be no doubt that this will be a valuable help to workers in the field. The present volume covers publications up to the end of 1954, but it is promised that supplementary volumes will appear.

J. D. N. NABARRO.

ARTISTIC SCIENTISTS

Art and the Scientist. By Geoffrey Lapage, M.A., M.Sc., M.D., M.Inst.Biol. (Pp. 115+xii; illustrated. 42s.) Bristol: John Wright and Sons Ltd. 1961.

This admirable book is a study of illustration in works of botany, zoology, and anatomy. The author's chief concern is with those scientists who actually made their own woodcuts, etchings, or engravings or who actively supervised the artists who worked for them. He gives an interesting historical survey of these scientists and their illustrations from the sixteenth century to the early twentieth century—from Leonardo da Vinci to Philip Henry Gosse, and from Vesalius to Henry Vandyke Carter, who made the drawings for the first edition of Henry Gray's *Anatomy* published in 1858.

The book is beautifully illustrated, containing eighteen reproductions in the text and twenty-two plates, eight of them coloured. Some of these are well known enough, but it is a pleasure to look again, in the company of Dr. Lapage, at the work of Robert Hooke, Ernst Haeckel, Ruini and Stubbs, Gosse and Bewick. There may be medical readers unfamiliar, as I was, with the drawings of many scientists reproduced here, for Dr. Lapage has ranged widely in his selection.

The author discusses the scientific and artistic qualities of these illustrations, and from this discussion he proceeds to consider what impels the scientist and the artist to their achievements. Here he follows the philosopher Alexander in agreeing that the impulse of the scientist is a manifestation of curiosity while the impulse of the artist is a manifestation of constructiveness. The difference between them is that the scientist "mixes his mind" with his observed facts and constructs a hypothesis from them, while the artist takes materials from the real world and combines them in a unity which adds to them some thought or feeling of his own; so that while the "truth made by the scientist will be the same for every man, the art made by the artist will be different from that made by every other artist." The scientist who illustrates his own observations then becomes, legitimately and necessarily, an artist who adds something of himself to these observations.

Dr. Lapage has written an interesting and erudite book which will give pleasure to many readers. It is a treatise neither dull, difficult, nor expensive.

D. V. HUBBLE.

MEDICAL PHARMACOLOGY

Medical Pharmacology. Principles and Concepts. By Andres Goth, M.D. (Pp. 551; illustrated. 82s. 6d.) St. Louis, Missouri: The C. V. Mosby Company. London: Henry Kimpton. 1961.

When knowledge in physiology, biochemistry, and pharmacology increases so quickly, the selection of material for teaching becomes extremely difficult. In the United States it is common for each member of the staff of a department to give one or more lectures in the field with which he is most familiar. The other members of the staff then attend to hear what he has to say, and as a result it often happens that the lecturer deals mostly with very recent advances. The lecture may then be above the heads of the students.

The only informative approach in teaching is historical. A science is an accumulation of observations made by workers who follow after one another, and the development of a particular theory is the outcome of steps which succeed one another logically. Only when he understands the logical sequence does the student obtain a grasp which is likely to remain in his mind for any length of time. No matter how much further the subject advances he has some chance of remembering the position as it was when he was a student.

If the historical approach is the only approach for the lecturer, how much more is it the right approach for the textbook. In the United States there are at least three very large textbooks of pharmacology, one of which each student attempts to read. These books are unsuited as textbooks for study because of their size, though they are excellent as works of reference.

The book under review is smaller, and will certainly attract some students for this reason. It is, however, superficial in its treatment, and fails to provide any historical approach. The development of the theory of the chemical transmission of nervous impulses forms the basis which explains the actions of agents of several kinds. No account of it is given, and in this connexion it may be pointed out that nicotine, a key substance in understanding the history, does not even appear in the index.

Pharmacology makes sense for the doctor when it is treated as a branch of physiology and the physiological basis of the action of drugs in the body is considered. In this sense pharmacology still flourishes in Western Europe. Unfortunately the references in the book are almost all to American journals.

J. H. Burn.

CLINICAL CHEMISTRY CONGRESS

Proceedings of the Fourth International Congress on Clinical Chemistry. Edinburgh, 14th to 19th August, 1960. Edited by C. P. Stewart, P. C. Jocelyn, S. C. Frazer. (Pp. 211+xvi; illustrated. 35s.) Edinburgh, London: E. and S. Livingstone Ltd. 1961.

In 1960 the Fourth International Congress on Clinical Chemistry was held in this country in Edinburgh. It consisted of symposia and communications. The titles of the four symposia were: "Plasma Protein Turnover and Disease," "Mechanisms of Urine Production," "Enzymes in Clinical Chemistry," and "Congenital Abnormalities of Metabolism." These are four problems towards which the interest of all chemical pathologists is turned at the moment.

A. S. Macfarlane (London) gave a general survey of the "turnover" of proteins, and he was followed by the Danish workers M. Schwartz and S. Jarnum, who reported on the measurement of the turnover of iodine-labelled proteins.

A very important contribution was presented by H. Wirz (Basle). It was a full exposition of the theory of urine production, involving in the renal tubules a counter-current multiplier system. F. Wroblewski (New York) explained the multiplicity of enzymes composing what we generally assumed to be a single enzyme—serum lactic dehydrogenase. Just as no one nowadays speaks of serum phosphatase in general but subdivides according to *p*H optima into alkaline and acid phosphatases and then proceeds to subdivide the acid phosphatases according to whether they are sensitive to formaldehyde, so will future refined methods subdivide most of the serum enzymes not only according to the substrate on which they act but also according to the tissue from which they originate.

The congenital abnormalities of metabolism affect all aspects of chemical pathology, but of particular interest are the surveys by H. Harris (London) on enzyme formation using pseudocholinesterase as an example, and by E. Beutler (California) on the two red-cell abnormalities — deficiency of glucose-6-phosphate dehydrogenase and galactosaemia.

It is impossible to name all important contributions to the symposia, and the reader will find plenty of stimulating facts in those not mentioned here and in some of the short abstracts of communications. He will be helped by an authors' index and the comprehensive subject index.

The value of this book can be summarized best by quoting the first paragraph of its preface: "An international scientific congress is more than merely an occasion for the presentation and discussion of the results of recent research; it is an opportunity for the assessment of progress, and in fields in which advance is especially rapid such assessments can most fruitfully be made by means of symposia, whose contributors should be men of eminence. It is also an opportunity for the younger scientist to assess the dimensions of his chosen subject, and (in the words of the Principal of the University of Edinburgh, Sir Edward Appleton) such a congress may fairly be described as 'a peripatetic university.'"

The organizers of the congress and the editors of its *Proceedings* deserve our thanks for having set such a high standard.

H. Lehmann.

CEREBROVASCULAR DISEASE

Pathogenesis and Treatment of Cerebrovascular Disease. Seventh Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Center, Houston, Texas. Compiled and edited by William S. Fields. (Pp. 562+xii; illustrated. £6.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

This book contains the proceedings of the symposium of the Houston Neurological Society held in the Texas Medical Centre in March, 1959.

It is divided into four parts: anatomy; occlusive disease; intracerebral haemorrhage; and subarachnoid haemorrhage and intracranial aneurysm. In the second section pathogenesis, mechanism of thrombosis, clinical syndromes, and medical and surgical treatment are presented, and the discussion after each

paper is included also. Cerebral haemorrhage is extensively covered, with special emphasis on intracranial aneurysms. Particularly impressive are the results of arterial reconstruction for occlusive disease of the innominate, carotid, subclavian, and vertebral arteries by De Bakey and his group from Houston. This section is clearly and lavishly illustrated, and excellent reproductions of cerebral arteriograms abound.

There is a great deal of factual detail, and though at times the text is perhaps a little too discursive the editor, Dr. W. S. Fields, is to be congratulated on his efforts, for this book will undoubtedly be of great value to all who are interested in the cerebral circulation. The format is excellent and the illustrations of high quality.

The price is rather high, and the usefulness of the book might have been increased by a simpler format at lower cost with earlier publication.

J. F. Goodwin.

HISTORY OF NURSING PROFESSION

A History of the Nursing Profession. By Brian Abel-Smith. (Pp. 290+xiv; illustrated. 30s.) London, Melbourne, Toronto: Heinemann. 1960.

This book is not a general history but deals specially with the social, economic, and political history of the nursing profession in England and Wales. It is largely factual. It is confessed, however, that "facts do not speak for themselves" and the warning is given that "by their selection and presentation the reader is influenced to accept the viewpoint of the writer." Yet it is clear that a sincere and for the most part successful attempt has been made to be impartial. The author has read very widely and tapped all available sources of information so that his work will need to be read and referred to by all who have anything to do with the training and welfare of nurses.

After dealing briefly with the early days of nursing the author continues with a description of the gradual introduction of the special training of nurses. This leads up to an excellent account of the long and bitter struggle for registration. (It is the first time that such a candid and revealing account of that unfortunate struggle has been printed in a book.) The latter part of the book is taken up with the political and economic problems which have vexed the profession during the last four decades. The shortage of nurses, perhaps over-emphasized, is attributed partly to the policy of the leaders of the profession and partly to other factors both inside and outside the nursing world. One of the most interesting chapters is the sixteenth, in which the author to a certain extent reveals his own opinions. There are three appendixes, chiefly statistical.

The book is well documented, but the references (over 1,000 in number) are put at the bottom of the page where they mingle with quotations and comments which should not be missed. For example, at the time when nurses at the Middlesex Hospital had to wear skirts with a train they sometimes turned up the hems, but the matron, Miss Thorold, would not allow this, for, she said, "I devised this little train so that when you lean over a bed to attend a patient your ankles will be covered and the students will not be able to see them." That incident contains a volume of social history.

Zachary Cope.

SURGERY OF INJURED HANDS

Injuries and Infections of the Hand. By Robert H. C. Robins, M.A., M.B., B.Chir., F.R.C.S. (Pp. 220+xii; illustrated. 63s.) London: Edward Arnold (Publishers) Ltd. 1961.

This book records Mr. Robins's special interest in hand surgery over a period of 11 years. Though he presents it as "a guide to the treatment of injuries and infections of the hand for surgeons having responsibility for them in casualty and accident departments," the book throughout bears the imprint of a very practical and well-read surgeon.

For example, in the section, "Planning of Treatment," he writes: "I cannot emphasize too strongly that the fate of an injured hand is usually decided at the first operation and this should not be begun until a plan is decided." Yet one wonders how many hand operations are still undertaken at casualty department level without a plan. The old edict to "preserve everything" dies very hard and the best chance of preserving a functioning hand is lost.

Hands being the most active and exposed members of the body they are its most frequently injured and infected areas. Such is the volume of work resulting from this that the majority of the load must continue to be borne by residents in casualty and accident departments. Mr. Robins has very clearly described all the common injuries and infections of the hand and sound methods for their treatment. The book, therefore, is of very great value to those most in need of guidance—namely, hospital residents.

Against this background one has two minor points of criticism. Though the position of function is well described, insufficient emphasis is placed on the importance of maintaining the metacarpal arch when immobilizing in plaster is necessary. One still sees too many plaster casts with all the metacarpals in the same flat line. This generally results from an effort to achieve a smooth palmar surface of the plaster during its setting phase: the heads of the fourth and fifth metacarpals are pressed back and as a result the metacarpophalangeal joints are extended. If the hand is immobilized in this position, fingers, particularly in the middle aged, become stiff. Mr. Robins favours the Fisk hand splint as an invaluable "silent assistant" in most hand operations; one wonders if the Rank and Wakefield hand stand is not to be preferred.

I have enjoyed and benefited from reading this excellently written, comprehensive, and well-illustrated treatise on common hand injuries and infections. Without qualification I recommend it to all surgeons, young and old, who are responsible for the care of the injured and/or infected hand.

William Gissane.

DAY HOSPITALS

The Day Hospital Movement in Great Britain. By James Farndale, B.Com., F.H.A., M.R.S.H. (Pp. 430; illustrated. 84s.) London: Pergamon Press. 1961.

In 1958 to 1959 Mr. Farndale, a professional hospital administrator working under the auspices of the Manchester University Department of Social Administration, undertook a survey of the psychiatric and geriatric day hospitals and day centres in Great Britain.

This book gives a very comprehensive account of Mr. Farndale's findings and conclusions. In all he visited 65 day hospitals and centres. Thirty-eight of these were devoted to the treatment of psychiatric patients, ten to

geriatric patients, and the remainder were for the mentally subnormal, the handicapped, or were concerned with various aspects of physical rehabilitation. The first part of the report surveys different aspects of the day-hospital movement and the second part gives a detailed account of each day hospital or centre which he visited. He discusses the physical facilities, the treatment activities, the staffing, and many other practical aspects of the running of these units. He gives details of the different practices regarding provision of drugs, meals, and transport, and summarizes all the available data on the financial aspects.

It is evident from this report that this development has taken place in a comparatively few areas—for example, London, Birmingham, Bristol, and Manchester. Elsewhere progress in this direction has been scanty or non-existent. One surprising fact is how little growth of this sort was found to have taken place in general hospitals devoted to undergraduate teaching. Only in Glasgow was a day centre to be found within such a general hospital and only in Manchester and Sheffield were there detached units associated with teaching hospitals.

This will prove a most useful reference book for any board of governors, regional board, or management committee planning to establish day hospitals or centres. It will be unfortunate if its extremely high price prevents it having the sale it deserves.

G. R. HARGREAVES.

LEPROSY

Notes on Leprosy. By Dharmendra, M.B., B.S., D.B.(Lond.). (Pp. 203+vi; illustrated. No price.) New Delhi, India: The Ministry of Health, Government of India. 1960.

This volume has been compiled from lecture notes prepared for delivery to students taking the postgraduate course in tropical medicine at the Calcutta School of Tropical Medicine, of which the author was head of the leprosy department. It is his intention to prepare a textbook on the subject, but in the meantime he has deemed this material worthy of publication as it stands.

With many misprints, devoid of both an index and references, and with an extraordinary numeration of the many tables and figures, this book, despite its obvious and admitted shortcomings, is a valuable publication. In the text there is a wealth of information on the fundamentals of leprosy. The author's wide knowledge and experience of his subject are reflected in the simple clarity with which this account of it is set out. As is to be expected, his presentation is for Indian students and so it is solely concerned with the forms of leprosy endemic in that subcontinent. The variations and peculiarities that leprosy can assume in other parts of the world receive little or no attention; but as an introduction to the disease, and as a reference book for the practitioner dealing with it, this work is admirable. The illustrations, whether line drawings, photogravures, or colour, are excellent. A valuable feature is the clinical differentiation of leprosy from other diseases readily confused with it. Last, but by no means least, is the practical advice on the handling of patients with the disease and a consideration of the defects and limitations of the existing legal enactments for control of the infection in India. Student, practitioner, and advanced worker all can profit from a perusal of these pages.

A. R. D. ADAMS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Chemotherapy of Tropical Diseases. By Sir Philip Manson-Bahr, M.D., F.R.C.P., D.T.M.&H.(Cantab.), and John H. Walters, M.D., F.R.C.P., Lieutenant-Colonel, I.M.S.(retd.). (Pp. 164+xi. 56s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Bile Pigments in Health and Disease. By C. H. Gray, M.D., D.Sc., F.R.C.P., M.R.C.S., F.R.I.C. (Pp. 101+x. 40s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Befinden und Verhalten. Verhaltensphysiologische und anthropologische Grundlagen der Psychopharmakologie. By J. D. Achelis and H. v. Ditfurth. (Pp. 110; illustrated. DM. 14.80.) Stuttgart: Georg Thieme Verlag. 1961.

C. G. Jung. By E. A. Bennet. (Pp. 165+viii; illustrated. 21s.) London: Barrie and Rockliff. 1961.

Logan Turner's Diseases of the Nose, Throat, and Ear. Edited by John P. Stewart. Sixth edition. (Pp. 524+xiv; illustrated. 52s. 6d.) Bristol: John Wright and Sons Ltd. 1961.

Human Pituitary Gonadotropins. A Workshop Conference. Edited by A. Albert, M.A., Ph.D., M.D. (Pp. 434+xi; illustrated. £6 14s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Zur Problematik der Multiplen Sklerose. By F. Georgi, P. Hall, H. R. Müller. (Pp. 123; illustrated. Sw. Fr. 27.) Basle, New York: S. Karger. 1961.

Essentials of Neurosurgery for Students and Practitioners. By Sean Mullan, M.D. (Pp. 273+xi; illustrated. $6.75.) New York: Springer Publishing Co. Inc. 1961.

Clinical Diagnosis. A Textbook of Physical Signs and Symptoms for Medical Students and Practitioners. By Rustom Jal Vakil, M.D.(Lond.), F.R.C.P.(Lond.), F.A.C.C., F.A.P.H.A., F.R.F.P.S., F.C.C.P., F.C.P.S., F.A.Sc., F.N.I., and Aspi F. Golwalla, M.D., F.C.P.S., F.C.C.P. (Pp. 412+xxi; illustrated. 60s.) London: Asia Publishing House. 1961.

David Edwardes—Introduction to Anatomy 1532. By C. D. O'Malley and K. F. Russell. (Pp. 64. 15s.) London: Oxford University Press. 1961.

A Manual for Nuclear Medicine. By E. R. King and T. G. Mitchell. (Pp. 406+x; illustrated. £5 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

The Parathyroids. Proceedings of a Symposium on Advances in Parathyroid Research held at the Rice Institute, now Rice University, Houston, Texas. Edited by Roy O. Greep, Ph.D. (Pp. 473+xvii; illustrated. 98s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Atlas and Demonstration Technique of the Central Nervous System. By James B. McCormick, M.D., F.C.A.P. (Pp. 99+vii; illustrated. 90s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

The Ship Would Not Travel Due West. By David Lewis. (Pp. 154+xii; illustrated. 21s.) London: Temple Press Ltd. 1961.

Patterns of Care. By Kenneth Robinson, M.D. (Pp. 42. 2s. 6d.) London: National Association for Mental Health, 39 Queen Anne Street, W.1. 1961.

Christian Samuel Hahnemann. By Rosa Waugh Hobhouse. (Pp. 55. 5s.) Rochford, Essex: C. W. Daniel Co. Ltd. 1961.

Chemistry of Cancer Toxin: Toxohormone. By Waro Nakahara, Ph.D., M.D., and Fumiko Fukouka, M.D. (Pp. 75+xiv; illustrated. 34s.) Springfield, Illinois: Charles C. Thomas. 1961.

A History of Thoracic Surgery. By Richard H. Meade, B.S., M.D. (Pp. 933+xx; illustrated. £11.) Springfield, Illinois: Charles C. Thomas. 1961.

Fluphenazine in Anxiety and Tension. Edited by W. W. Heseltine. (Pp. 92+xiv. 15s.) Liverpool: Charles Birchall and Sons Ltd. 1961.

Obstetrical Endocrinology. By Jose Botella-Llusia, M.D. (Pp. 129+x; illustrated. 52s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Mediatrics. By H. F. Ellis. (Pp. 86; illustrated. 10s. 6d.) London: Geoffrey Bles. 1961.

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CAUSES OF BRONCHIAL CANCER

Since the epidemiological evidence was published pointing to the smoking of tobacco as a cause of lung cancer[1-3] and of other diseases[4-6] the search for direct biochemical or pathological links has been intense, and it is yielding results.

In man carcinoma of the bronchus usually arises in the epithelium of the extrapulmonary tracheobronchial tree after a period of thirty years or so of habitual smoking, during which time the mucosa is subjected for several hours every day to what is thought to be a very low and perhaps subcarcinogenic dose of a carcinogenic hydrocarbon. This hypothesis immediately recalls the pioneer experiments of Peyton Rous on what is now called "co-carcinogenesis." During relatively long periods of time he applied a carcinogen to the skin of rabbits in small and carefully graduated subcarcinogenic doses. This produced a series of multiple, scattered, innocent, hyperplastic lesions of the epithelium. He described the areas of skin so treated as "initiated" and was able to "promote" carcinoma in them by non-carcinogenic irritants or by simple trauma. His experiments were strictly quantitative as regards the periods of initiation and the doses of carcinogen used.

If the course of human bronchial cancer follows this sequence of initiation and promotion it should be possible to show that the bronchial mucosa of many habitual cigarette smokers undergoes progressive but innocent epithelial hyperplasia, that the areas of epithelial instability increase in number and intensity with the length of exposure and the number of cigarettes smoked per day, that the same changes are never seen in the bronchi of non-smokers whose occupation carries no risk of bronchial cancer, and that the mucosa of an overwhelming majority of cases of bronchial cancer clearly shows, in areas free of malignant infiltration, the same variety of hyperplasia. To forge these links in the chain of evidence which relates cigarette smoking to bronchial cancer is a formidable task. The total area of respiratory epithelium at risk is surprisingly large. The areas of epithelial instability would, in all probability, be microscopic in size and widely scattered, and no accurate correlation could be expected unless thousands of histological sections from hundreds of specimens of mucosa from the main bronchi and their 24 or so extrapulmonary branches were critically examined by a competent observer.

Four years ago O. Auerbach and colleagues published a progress report from New Jersey, U.S.A., on an investigation which started in 1954.[7] The tracheobronchial tree of 117 male patients dying with or without bronchial cancer was examined histologically. A total of 24,336 sections (an average of 208 from each specimen) was examined histologically. Microscopic foci composed of proliferating bronchial epithelium were found scattered over the whole of the extrapulmonary bronchial mucosa. In some lesions there were relatively few atypical cells; in others of larger size the whole cell population was atypical. There were all gradations between these extremes. There was a close association between the occurrence of these scattered areas of hyperplasia and a history of habitual cigarette smoking. They were very rarely found in non-smokers. They were more numerous, more cellular, and contained more atypical cells in patients dying of bronchial cancer. In the most cellular lesions the atypical cells had broken through the epithelial basement membrane.

Since 1957 the investigation has progressed and the results of the extended inquiry have recently been published and combined with those of the progress report.[8] The number of sections examined from each specimen has been reduced to 58, and after eliminating preparations which were unsuitable for histology 19,797 sections in this series were examined by one pathologist who throughout the whole inquiry had no knowledge of the identity of any section. The results obtained from this larger second series fully confirmed the association between widespread instability of the cells of the bronchial mucosa and habitual cigarette smoking. They revealed a similar association between bronchial cancer and an increased incidence of larger and more cellular hyperplastic lesions composed entirely of atypical cells. They also strengthen the supposition that bronchial cancer may be related to co-carcinogenesis and that the stimulus which propels the initiated mucosal epithelium into malignancy may be non-carcinogenic. The suggestion that denudation of the epithelial lining resulting from infection may provide the promoting stimulus may therefore be less speculative than appears at first sight.

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[2] Doll, R., and Hill, A. B., *Brit. med. J.*, 1950, **2**, 739.
[3] —— —— ibid., 1952, **2**, 1271.
[4] —— —— ibid., 1956, **2**, 1071.
[5] Lowe, C. R., ibid., 1956, **2**, 1081.
[6] See *Brit. med. J.*, 1960, **2**, 1077.
[7] Auerbach, O., *et al.*, *New Engl. J. Med.*, 1957, **256**, 97.
[8] —— Stout, A. P., Hammond, E. C., and Garfinkel, L., ibid., 1961, **265**, 253.

Two contributions to the relation between smoking and other pathological changes appear in the *Journal* this week. Drs. R. M. Acheson and W. J. E. Jessop report (p. 1107) that in a series of elderly men tobacco smoking was found not to be associated with increased cholesterol or lipoprotein in the serum. This agrees with the hypothesis that the causes of coronary thrombosis are apt to be different in young and old men. In this issue also Drs. J. Read and T. Selby report (p. 1103) their finding of decreased ventilatory capacity of the lungs among smokers.

MANAGEMENT OF FRONTAL SINUSITIS

Now that infections of the upper respiratory tract are gathering force sinusitis will be frequently seen in practice. Frontal sinusitis, though not as common as maxillary sinusitis, has the more dangerous complications. The usual organisms causing the infection are the common secondary invaders—namely, streptococci (aerobic and anaerobic), pneumococci, staphylococci, *Haemophilus influenzae*, and Friedländer's bacillus. Among the precipitating causes of sinusitis during an upper respiratory infection are invasion by particularly virulent strains of such organisms, reduced local and general resistance of the patient, diving, swimming, nasal douching, and barotrauma.

The lesion in the frontal sinus may be solitary or a part of a pansinusitis with symptoms referable to one or both frontal sinuses. Typically the patient is pyrexial and locates the pain with one or two fingers only, pointing to the site of the frontal sinus. He is tender to percussion over the anterior wall of the sinus, and especially so to pressure exerted on the sinus floor. In milder cases the patient during or after a cold may complain of a similarly localized pain coming on two to three hours after rising and wearing off again in a few hours. A purulent nasal discharge does not usually appear until the oedema of the fronto-nasal duct subsides to release the pent-up pus from the sinus.

In most mild cases recovery follows rest in a warm room and the use of a ½% ephedrine nasal spray. In severe cases the patient requires treatment with an antibiotic or chemotherapeutic agent in adequate dosage until full recovery.

Provided the diagnosis is correct and complete a failure to respond to adequate treatment indicates that the infecting organism is insensitive to the drugs given, and under these circumstances the frontal sinus should be drained. Surgical drainage is performed through the thin cortical bone of the sinus floor to avoid the fronto-nasal duct, and antibiotic therapy is changed to suit the sensitivity of the organisms found. A drain is left *in situ* until the fronto-nasal duct can be shown to be functioning satisfactorily.

Delay in recovery, relapse, or recurrence of the sinusitis may be due to a combination of infective and mechanical factors obstructing the fronto-nasal duct—for example, chronic maxillary or ethmoid sinusitis, nasal polypi, deflected nasal septum, cyst of the middle turbinate, and osteoma. These associated lesions require surgical treatment once the acute lesion is under control. Another factor not to be overlooked is that the acute lesion may indeed be an acute exacerbation of a chronic frontal sinusitis. A total obstruction of the fronto-nasal duct together with sinusitis may produce a mucocele or pyocele in the chronic case. Mucoceles and pyoceles frequently destroy the thin sinus floor and present as an orbital swelling producing a forward, downward, and outward proptosis. A sign of many of these indolent lesions is a swollen upper eyelid due to acute exacerbation of chronic frontal sinusitis. If a pyocele ruptures on to the skin surface a fistula develops. As a rule any fistula at the inner canthus above the level of the medial tarsal ligament communicates with a pyocele of the frontal sinus. In these cases the acute lesion must be controlled, the associated lesions obstructing the fronto-nasal duct removed, and the pyocele excised by an external fronto-ethmoidectomy or an osteoplastic frontal bone flap.

Severe sinusitis will cause, and delays in diagnosis or inadequate therapy will permit, a local or general osteitis of the skull to develop with subsequent "rupture" of the frontal sinus either through the thin cortical bony floor or the cancellous bone of the anterior wall to produce a swelling of the upper eyelid or forehead. In spite of normal radiological findings (for bone changes are not demonstrable for at least seven to ten days) this must be regarded as an osteitis of the skull and brought under control quickly if sequestration of bone is to be prevented and intracranial complications avoided. The intracranial complications which may ensue are meningitis, extradural and subdural abscesses, abscess of frontal lobe, and thrombosis of superior longitudinal sinus. All of these may also arise from frontal sinusitis by spread of thrombophlebitis without an intervening obvious osteitis. A failure to recognize these complications early may delay recovery or lead to the death of the patient. They may occur singly or in combination. The diagnosis can often only be

suspected and not worked out in detail at a time when treatment is most effective.

Patients with frontal sinusitis who are unwell and whose local pain has become a diffuse headache frequently have an intracranial complication. Vomiting does not occur with sinusitis alone, and when associated with headache it indicates that the patient has an extradural abscess at least and perhaps more. Papilloedema is not an early sign of an intracranial suppuration, for it takes at least two to three weeks to develop. A rigor or high swinging temperature and high pulse rate suggest a thrombosis of the superior longitudinal venous sinus, and an epileptiform fit frequently means the onset of a subdural abscess. Drowsiness progressing to coma occurs with cerebral thrombophlebitis, meningitis, and abscess of frontal lobe. The frontal lobe is a silent area and localizing physical signs are usually absent. In meningitis neck rigidity may not appear for 48 hours or more. Frontal lobe abscess is still a persistent killer, for it is often diagnosed late or not at all. It is preceded by a cerebral thrombophlebitis of two to three days' duration, and proper treatment at this stage may produce resolution of the lesion before suppuration occurs. It should be possible from the symptoms to suspect the presence of an intracranial lesion within 48 hours of its onset, and the institution of vigorous treatment may lead to a higher rate of recovery from these serious complications of disease in the frontal sinus.

HEALTH AND WEALTH

If dialectical skill were the first quality needed in a Minister of Health there can be no doubt that Mr. Enoch Powell outstrips all his predecessors in this respect. His brilliant disquisition in the Lloyd Roberts Lecture at the Royal Society of Medicine last week was, we may be sure, meant to be more than a forerunner to this conclusion towards the end: "The expenditures on this country's public financed health services over the next three or four years will, it is intended, be allowed to rise in total at a rate not exceeding about 2½% per annum." But he took the precaution to add that "it would be a travesty to think that 2½% per annum represents in any way the advance which these services can, should, or will make in the same period." The subject of Mr. Powell's address was "Health and Wealth." He tackled the popular conclusion that the greater outlay on the care and treatment of sickness would increase the country's wealth. Even if there were some positive causal relationship between gross domestic product by head and outlay on the care and treatment of sickness, this could, Mr. Powell said, apply only within certain limits. Vaccination and immunization were examples of what Mr. Powell called money-spinners in the short term. Expenditure on the weakling, the old, the subnormal, would obviously not increase the gross national product. But, as Mr. Powell pointed out, the economically justifiable elements of a health service are inextricably bound up and grow up with the rest. He sees much of the progress of medical science as being "not in doing things more cheaply and simply than before but in discovering complex and difficult things to do which previously could not be done at all. On these fronts medicine is buying life at an ever increasing marginal cost." He describes as a "miscalculation of sublime dimensions" Lord Beveridge's estimate (in 1942) that the outlay on the Health Service would not rise over 20 years, quoting this passage from the Beveridge Report: "'It being assumed that there will actually be some development of the Service, and as a consequence of this development a reduction in the number of cases requiring it.'" Mr. Powell, too, looks upon the statement in the Guillebaud Committee's Report—"the National Health Service is a wealth-producing as well as a health-producing Service"—as a perpetuation of the same fallacy.

The history of medicine, we suggest, gives ample support to the conclusions of the Guillebaud Committee, and possibly the sublime miscalculation which Mr. Powell lays at Lord Beveridge's door should be directed at his estimate of "20 years." Both probably err in talking in terms of a service. If the progress of medical science in prophylaxis continues, and if research into cancer, for example, and such cardiac conditions as strike people down in their prime goes ahead, then the Beveridge prediction may come true, but not in the time he allowed for it. Mr. Powell's brilliance as a dialectician should not divert our eyes from his one positive statement that the expenditures on this country's publicly financed health services will not go above 2½% per annum in the next three or four years.

THE WRONG PATIENT

Twice[1 2] in recent years the Medical Defence Union has had occasion to give a special warning in this journal about operating on the wrong patient or the wrong part of him. These mistakes are certainly very rare in proportion to the enormous numbers of operations performed, and fortunately some of them (for example, removal of the wrong finger-nail) are a cause of serious inconvenience to the patient rather than catastrophe. But the same lack of scrupulous care that leads to a minor mistake can equally cause one that will be a haunting reproach to the surgeon and a disaster to the patient. Consequently the Medical Defence Union and the Royal College of Nursing have now prepared a joint memorandum (see page 1157) suggesting ways to obviate the risk of such errors. It begins by stating: "These avoidable mistakes are quite indefensible." The main idea underlying the recommendations put forward here is the labelling and marking of the patient before

[1] Forbes, R., *Brit. med. J.*, 1955, 2, 851.
[2] Addison, P. H., ibid., 1960, 2, 806.
[3] French, P. R., ibid., 1960, 2, 940.
[4] Watson-Jones, R., ibid., 1955, 2, 968.
[5] Addey, W., ibid., 1955, 2, 1089.

he reaches the operating-theatre. All unconscious patients, the memorandum suggests, should be labelled before they are taken to the wards, and all patients should be labelled before they go to the operating-theatre. While this is intended to ensure that the right patient reaches the operating-table another set of recommendations is designed to ensure that the surgeon operates on the right part. The basic safeguard suggested is that the side on which the operation is to be performed should be indelibly marked on the patient's forehead before he reaches the theatre. It may be preferable to go further and put one or more additional marks near the part to be operated upon.[3] The numbering of fingers and toes is once again discussed as it has been from time to time in this journal,[4 5] together with the need for legible notes and writing out the words "left" and "right" in full.

No doubt many hospitals already use some or all of these safeguards, and they set an example that could be universally followed. The memorandum reports that during two years in 1959–61 the Medical Defence Union alone dealt with 28 cases of this kind of mistake, and undoubtedly further cases came to the attention of the two other defence societies, so that the need for action is clear enough. More ideas of assistance to hospital staffs may come out of a meeting of representatives from all three societies on October 27 in London.

PREVENTION OF CHRONIC DISEASE

"Practical Steps in the Prevention of Chronic Disease" is the special subject chosen for discussion by the Divisions and Study Group of the B.M.A. during the session 1961–2. This is the sort of everyday theme of wide scope which often tends to be unjustly neglected. The steering committee appointed by Council under the chairmanship of Sir Francis Fraser "to initiate, guide, and finally to collate the results of discussions" has prepared a useful leaflet to guide those who intend to take part in what Sir Francis calls "this country-wide co-operative study." The leaflet explains that the object of discussion is primarily to gather together suggestions by groups of doctors on practical steps for reducing the incidence, duration, and severity of chronic disease. But the extent of the possible field of inquiry has led the steering committee to advise each Division or Group to select for study one disorder from each of the two main categories of "major" and "minor." The major disorders are: arteriosclerotic and degenerative heart disease; hypertension; chronic bronchitis; peptic ulcer; chronic gynaecological disease; and disk lesions and back and other strains. The minor disorders are: upper respiratory catarrh; dental disease; obesity; postural disorders, including deformities of the feet; acne; and constipation. These subjects are admirably chosen and, as Sir Francis Fraser mentions in his foreword to the leaflet, new knowledge of the pathology and aetiology of these disorders might well be acquired from following up any promising clues suggested at the discussions. The steering committee also hopes that all Division and Study Groups will try to find the right answer to one general and controversial question: "Are periodic medical examinations of the apparently healthy desirable as a means of early detection and prevention of chronic disease?"

The first "subject of the year"—adolescence—occupied the attention of a relatively small number of Division and Study Groups two years ago, but the report[1] issued earlier this year was recognized as a sensible contribution to a subject which is often submerged under emotional waves of popular opinion. Last year the subject of "Health Education" attracted the attention of 43 Divisions and Groups, and, as Council were informed this week, Sir Allen Daley and his steering committee are at present collating their findings. This year no doubt, as this new activity of the B.M.A. becomes more widely known, many more Divisions and Groups will wish to make their contribution to a report which should help doctors to tide patients over the temporary or permanent disabilities which afflict so many of them.

[1] *The Adolescent*, 1961. Obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1. Price 2s. 6d. net.

NOBEL PRIZE

The award of the Nobel prize for medicine to Dr. Georg von Békésy marks his outstanding contributions to the physiology of hearing. Trained in both physics and medicine, he is noted for the technical ingenuity of his experimental procedures. These entailed the use of specially devised micromanipulators, electrical recorders, and anatomical models.

Born on June 3, 1899, in Budapest, Dr. von Békésy studied at the University of Berne; at the University of Budapest, where he obtained the Ph.D.; and at the University of Münster, where he proceeded M.D. with honours. Until the end of the second world war his work was divided mainly between the Royal Hungarian Institute for Research in Telegraphy, where he was research investigator, and Budapest University. He also worked for a time in Berlin, and in 1947 at the Karolinska Institute, Stockholm. In 1947 he went to the U.S.A. and since 1949 has been senior research fellow in psycho-physics at Harvard University.

Dr. von Békésy's interest in the physiology of hearing is said to have begun when an economist asked him whether a major improvement in the quality of communication systems could be expected in the near future.[2] This set von Békésy asking himself, How much better is the ear than the telephone system? Moving easily among the mechanical and electrical concepts of physics together with the mathematics in which they are expressed he set about analysing the changes that take place in the auditory apparatus when it is stimulated by sound waves. Extraordinary ingenuity and much patience went into the devising of special apparatus for this purpose. He has noted, for instance: "Several years were required to develop the instruments needed to make direct measurements of the elasticity of the cochlear partition along its length, the precise form of the travelling waves for low frequencies, and the displacement of the place of maximum

[2] *J. acoust Soc. America*, 1961, 33, 1149.
[3] Békésy, G. von, *Experiments in Hearing*. New York. 1960.

amplitude for man and other animals." He then succeeded in studying detailed movements in the organ of Corti and constructed models which gave an analytical demonstration of these movements. Much of our knowledge of cochlear function stems from this work. An edited version of von Békésy's research papers (from which the above quotation is taken) appeared last year.[3]

CONGENITAL DEFICIENCY OF TRANSFERRIN AS A CAUSE OF HAEMOSIDEROSIS

Whereas it has long been accepted that man has a series of blood groups which are genetically determined, only in the last ten years has it become apparent that this is equally true of human haemoglobins, while in the last five years numerous genetically determined variations of protein in human plasma have been recognized.[4] In addition to the coagulation factors the plasma proteins include haptoglobins, the pseudocholinesterases, certain alpha$_2$-globulins, and the transferrins. Transferrin is the iron-binding globulin which, in conventional electrophoresis of plasma, forms part of the β-globulin fraction. The subdivision of the globulins has been carried far by the application of starch-gel electrophoresis and has led to the discovery of at least nine transferrins, all differing in their electrophoretic mobility.[5–9]

Recently a genetical abnormality has been described in which a deficiency of transferrin was thought to cause haemosiderosis. Two cases of transferrin deficiency with haemosiderosis but without a family study to support the supposition of a genetical rather than an acquired cause of the disease have been reported[10 11] and now L. Heilmeyer and his colleagues[12] have described a congenital deficiency of transferrin in a 7-year-old girl. A greatly reduced level of transferrin was also found in both parents. The presenting symptom was a severe hypochromic anaemia. The child died suddenly and it was thought that the heart muscle had been damaged by the deposition of iron and the anaemia. It was remarkable that the clearance time of the plasma iron was greatly shortened, yet incorporation of iron in the red blood cells was also much below normal. This indicated that iron was preferentially deposited in the liver, pancreas, heart, and other organs. Iron was apparently absorbed normally from the intestinal tract despite the absence of transferrin. To some extent it was even slightly above normal, though it did not approach the values usually found in iron-deficiency anaemia. Haemosiderosis is known to be in many cases a familial condition, and it seems possible that in some of these cases a genetically determined abnormality in the production of transferrin is the cause.

[4] Harris, H., *Brit. med. Bull.*, 1961, **17**, 217.
[5] Smithies, O., *Nature* (*Lond.*), 1957, **180**, 1482.
[6] —— ibid. 1958, **181**, 1203.
[7] Harris, H., Robson, E. B., and Siniscalco, M., ibid., 1958, **182**, 452.
[8] Giblett, F. R., Hickman, C. G., and Smithies, O. ibid., 1959, **183**, 1589.
[9] Harris, H., Penington, D. G., Robson, E. B., and Scriver, C. R., *Ann. hum. Genet.*, 1960 **24**, 327.
[10] Riegel C., and Thomas, D., *New Engl. J. Med.*, 1956, **255**, 434.
[11] Hitzig, W. H., Schmid, M., Betke, K., and Rothschild, M., *Helv. paediat. Acta*, 1960, **15**, 203.
[12] Heilmeyer, L., *Deutsch. med. Wschr.*, 1961, **86**, 1745.

PEPTIC OESOPHAGITIS

In recent years oesophagitis has become one of the commonest diagnoses made in dyspeptic patients. The main facts of the disease are now known and are worth rehearsing, for precision of diagnosis is essential to successful treatment. The symptoms are heartburn and retrosternal pain after meals and on lying flat at night, regurgitation of acid and food on stooping, and retrosternal discomfort on swallowing. The condition may be associated with pregnancy and can also occur in infancy. The mechanism of oesophagitis is clear: it is caused by the corrosive backwash of gastric juice into the oesophagus. Exactly how the cardia becomes incompetent to allow this reflux is uncertain, and indeed the mechanism by which it normally seals the oesophagus from the stomach is still a matter of research and argument. However, in the vast majority of patients peptic oesophagitis is associated with a sliding hiatus hernia.

The pathological correlation is not exact, for while changes are often seen at oesophagoscopy it is not uncommon for the oesophagus to appear normal despite unequivocal symptoms. The changes, when present, consist of linear, superficial ulceration along the crests of mucosal folds in the lower oesophagus and a ring of superficial ulceration at the oesophago-gastric junction. A true peptic ulcer is not seen unless the lower oesophagus is abnormally lined by gastric epithelium, a rare condition.[1]

The diagnosis is readily confirmed by radiology in most cases, when a sliding hiatus hernia and reflux of barium are seen. It is uncommon to see mucosal irregularity in the oesophagus, and the presence of oesophagitis must be inferred from the history or confirmed by oesophagoscopy. A word of caution is necessary, because hiatus hernias are commonly found in middle life and not all of them are causing symptoms. A hernia without symptoms is best ignored or it becomes the whipping-boy for all epigastric complaints.

Conservative treatment will control the symptoms of most patients with peptic oesophagitis. It occurs principally in the plump and middle-aged, and weight reduction is the cardinal point. How this works is mysterious, but it is, without doubt, most effective, and is usually accompanied by spontaneous reduction of the hernia and loss of reflux. In addition, alkalis should be prescribed liberally. There is also no doubt that nocturnal reflux, which may be the most damaging, can be minimized by the patient sleeping propped up. This advice is easily given, but a few extra pillows are often ineffective and a bed-rest or blocks beneath the head of the bed are preferable. When associated with pregnancy the condition is self-limiting, being completely relieved by delivery. The hiatus hernia of infancy carries a poorer prognosis, since two-thirds of the cases improve spontaneously while the remainder persist in having symptoms.[2]

[1] Barrett, N. R., *Brit. J. Surg.*, 1950, **33**, 175.
[2] Carré I. J., *Arch. Dis. Childh.*, 1959, **34**, 344.
[3] Wooler, G., *Gut*, 1961, **2**, 91.

In spite of this regime a few patients will have persistent symptoms, or complications may have developed before consultation. Haemorrhage may occur at any time, either occult or obvious, but this is rarely an indication for surgery by itself. The important complication is formation of stricture announced by increasing dysphagia; the treatment of it has always been unsatisfactory. G. Wooler[3] has just reviewed his experience of over 1,500 cases of oesophagitis; operation was performed in a third of them. On the problem of stricture he is encouraging. Small strictures can be dilated and the hernia satisfactorily repaired; it is where the stricture is long and the oesophagus shortened that difficulty arises. Wooler has found that, when the stricture feels soft on dilatation, the hernia can nearly always be reduced after extensive mobilization of the oesophagus within the chest, even to the extent of dividing both vagi. Eighteen cases have undergone this procedure with excellent results, a remarkable achievement. The alternative, and the only operation for tough, fibrous strictures, is resection with reconstruction by a jejunal implant. This may be a gratifying operation, but clearly the preservation of the patient's oesophagus should be the surgical aim.

THALASSAEMIA IN BRITAIN

Thalassaemia is an inherited anaemia affecting particularly the peoples of the Mediterranean seaboard from Sicily to Turkey. The affected persons have red blood-cells which are thinner than usual and appear in blood films as the so-called "target cells." These thin red cells have a relatively short life, so the patient becomes anaemic; the spleen enlarges, often becoming enormous, and engulfs still more red cells. Few affected patients survive to adult life. The thalassaemia trait is quite widespread; it rarely causes the carrier any trouble even though some target cells can be found in blood smears; such carriers are heterozygotes, inheriting the gene from only one parent. The patients with the fully developed syndrome are homozygotes, having inherited the abnormal gene from both parents. We also know that the formation of normal adult haemoglobin is defective in thalassaemia, and the defect is made up partly by persistence of foetal haemoglobin and partly by formation of an unusual fraction of normal adult haemoglobin, labelled haemoglobin A_2. In 1955 M. C. G. Israëls and R. L. Turner[4] in Manchester reported that they had found an inherited target-cell anaemia resembling thalassaemia in some ways in two British families who had no evidence of Mediterranean ancestry. The affected patients had persistently low haemoglobin levels of about 10.5 g./100 ml. (70%) and were resistant to haematinic treatment. Target cells were prominent in the blood smears, the red cells showed increased resistance to hypotonic saline, and some foetal haemoglobin was still present; on investigation other affected members of the families were found. This British target-cell anaemia differed from the typical Mediterranean form in two respects: the patients were only mildly affected—one did come for investigation of anaemia, the other was found when a blood count was carried out as part of an antenatal examination—and there was no splenomegaly.

Since 1955 other similar families have been reported in this country. C. W. H. Havard, H. Lehmann, and R. Bodley Scott[5] found three affected members of an East Anglian family. S. T. Callender, B. J. Mallett, and H. Lehmann[6] in Oxford investigated the families of three patients with this syndrome and detected 25 cases in all. They conformed with the original picture; most of them were symptomless and showed no abnormal physical signs, some had slight pallor; in none was anaemia severe; target cells were prominent in the blood films, and the osmotic resistance of the red cells was increased. Callender and her colleagues found that iron absorption was reduced in their original three patients. Investigation of the A_2 fraction of normal adult haemoglobin showed a distinct increase in all except one of the carriers. They consider that their patients "were clearly heterozygous for thalassaemia." One of their patients had had a Spanish ancestor three generations back, but the other two had no known link with Mediterranean ancestors.

These reports show that thalassaemia in heterozygous subjects can be considered in the differential diagnosis of patients with mild anaemia that is refractory to haematinic treatment. The diagnosis is settled by the presence of target cells in the blood film, the increased resistance in the saline fragility test, and perhaps the detection of other affected members of the family. If facilities are available for the estimation, the proportion of haemoglobin A_2 will be found to be increased. In Great Britain liver disease with jaundice is the only other likely cause for the presence of target cells in the blood, but the other associated haematological abnormalities do not occur. It is worth remembering that these patients are usually well accommodated to their 70% haemoglobin level and it is waste of effort to try to raise it. The records show that childbirth, for example, proceeds normally without undue strain on the mother.

[4] Israëls, M. C. G., and Turner, R. L., *Lancet*, 1955, 2, 1363.
[5] Havard, C. W. H., Lehmann, H., and Scott, R. B., *Brit. med. J.*, 1958, 1, 304.
[6] Callender, S. T., Mallett, B. J., and Lehmann, H., *Brit. J. Haematol.*, 1961, 7, 1.

LORD NUFFIELD'S GIFT TO B.M.A. LIBRARY

Lord Nuffield has added to his countless benefactions to medicine by giving £50,000 to the British Medical Association to be devoted to the extension and re-equipment of the Library at B.M.A. House. Lord Nuffield accepted honorary membership of the B.M.A. in 1936, and he gave evidence of his continuing interest in the Association when he declared open the new extension to B.M.A. House, known as the Burton Street site, in 1960.[1] This event is commemorated in a plaque in the building, and now Lord Nuffield's name will be associated with the Library, the much needed extension of which is made possible by his generous gift.

[1] *Brit. med. J. Suppl.*, 1960, 2, 55.

THE DESIGN OF LIFE-JACKETS

BY

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The properties of a serviceable life-jacket are various and depend upon the particular circumstances of use. Special needs impose special requirements. For example, a commando-soldier may carry much heavy metal equipment and may therefore need great additional buoyancy. A log-roller may be likely to be knocked unconscious as he falls into the water. Certain air-crew may be especially likely to be injured as they become cast-away.

Requirements

It is therefore difficult to generalize about life-jackets, but the following is an attempt. (1) A useful life-jacket should provide enough buoyancy to support a human being on the surface of fresh water. (2) The life-jacket should be easy to put on or should be so compact that it can conveniently be worn during periods of risk. (3) The life-jacket should be resistant to deterioration due to storage in various climatic conditions or to the stresses of use and misuse. (4) If possible, the life-jacket should allow the wearer to "swim" easily. (5) If possible, the life-jacket should support a weak or helpless man so that his mouth and nose remain clear of water without effort on his part.

The last of these requirements is probably of the least general importance, yet it gives rise to most discussion and argument.

Floating Position

There is emotional resistance to the thought of a life-jacket which tends to force the face under the water and which has to be countered by the activity of the cast-away. This aspect of the matter has received attention in the lay press.[1]

The International Convention on Safety of Life at Sea (1960) (Regulation 22)[2] "requires that a life-jacket shall not be approved unless it satisfies the following requirements: (*c*) It shall be so constructed as to eliminate so far as possible all risk of its being put on incorrectly, except that it shall be capable of being worn inside out. (*d*) It shall provide support to the head so that the face of an unconscious person is held above the water with the body inclined backwards from its vertical position. (*e*) It shall be capable of turning the body, on entering the water, to a safe floating position with the body inclined backwards from its vertical position."

The main reason why this matter of the floating position has caused so much discussion is that it is difficult to bring it to objective test. It is quite easy to determine, objectively, the total buoyancy of a life-jacket. It is fairly easy to determine its resistance to compression and abrasion or the effect of temperature, humidity, and micro-organisms upon its performance. Whether or not a life-jacket easily supports a person without effort on his part, in a safe position in rough water, remains a matter of opinion, and thus of argument.

In an attempt to overcome this lack of objectivity, Macintosh and Pask[3] made the assumption that if a life-jacket would support an inert, flaccid, unconscious man in a favourable way, it should also support a weak man in a good position, while requiring from him the minimum of exertion. They used, as their test object, a rather deeply anaesthetized man. The limitations of the technique were recognized. Such experiments cannot be carried out in real sea conditions, and only very few subjects could ever be tested. The subject used in Macintosh and Pask's tests was of a particular body build, not necessarily representative of the "median man." In their discussion they wrote:

> "The design of jackets so that they are comfortable, buoyant, robust, easy to inflate and adjust, able to carry ancillary equipment, etc., and yet allow the subject to swim, is properly the task of engineers.
>
> "The engineer needs medical assistance, however, because the human body contributes most of the buoyancy to the subject/life-jacket combination, so that the body's variations must be considered.
>
> "If dummies could be made, representative of the various types of men, women, and children, they would be of great help to engineers interested in this work. The dummies would have to be correct in weight, in total and distributed buoyancy, in the location of centres of gravity, and in flexibility."

With the publication of W.A.D.C. Technical Report 55–159[4] most of the data needed for the design of a "floating" dummy representing a 50-percentile man became available. In consequence of this publication, one or two firms in the United States manufactured moulds in which dummies could be cast to conform with the external measurements of the man whose major dimensions are midway between the extremes of size, and many dummies have been made for use in tests of aircraft equipment and for the investigation of car crashes.

The existing dummies of this 50-percentile man were in no sense designed to float as a man does. However, the existence of the data and of the moulds based upon it made feasible the construction of a "floating" dummy.

The Dummy

It is difficult to know how accurate such a dummy need be in order to be of service. It was therefore decided to make the first dummy as accurately as possible, despite the high cost. The following requirements were agreed.

1. Limb and trunk segments should conform to the correct external dimensions and have densities conforming to the best available data. The data on body-segment densities in W.A.D.C. Technical Report 55–159 are mainly derived from experiments on dismembered corpses. However, the density of the body segments probably did not differ greatly from normal even though, through disease, the volume and mass of the segments may have been different from the figures for the 50-percentile man. The most difficult decision concerns the lung-containing segments of the body. The cadaver segment densities were accepted because they probably correspond to the state of an inert man who does not attempt respiratory activity or glottic closure and thus allows air to be forced from his lungs by the pressure of water on his abdomen and thorax. The thorax and upper abdomen will be more buoyant in active men, but experimentally this can be allowed for by adding buoyancy chambers.

2. The centre of gravity of each body segment should be correctly placed. It was decided that the distribution

of mass within each segment should be as close to normal as possible. Thus it was decided that the skeleton of the dummy should approximate in density to bone and should be encased in "flesh" approximating to the density of human flesh. In dummies for other purposes strong and heavy steel skeletons had been used, and flesh parts were often of foam rubber. The skeleton for the floating dummy was accordingly constructed of plastic laminates, fibreglass, and a minimum of stainless steel at articulations (Fig. 1). The consequence of deciding the size and shape and density of each individual body segment, and then assembling them into a dummy, was that the total mass and total volume of the dummy would conform with known measurements from living men only if the predictions of segmental densities were reasonably correct. The design densities and the actual densities achieved are shown in Table I.

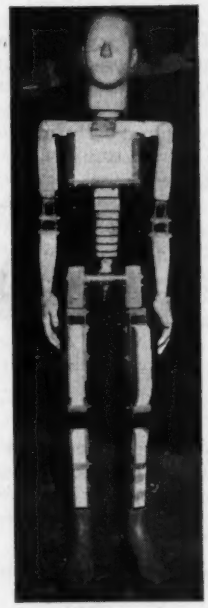


Fig. 1

Fig. 2

Fig. 1.—Skeleton for floating dummy. Fig. 2.—The completed dummy.

Table I.—*Design and Actual Densities*

Body Segment	Design Density	Actual Density	Design Percentage of Total Body Mass	Actual Percentage of Total Body Mass
Head	1·11	1·14	8·4	8·1
Upper arm	1·07	1·08	3·46	3·46
Forearm	1·12	1·13	1·61	1·61
Hand	1·12	1·13	0·54	0·54
Thigh	1·05	1·05	13·65	12·0
Leg	1·08	1·09	4·65	6·5
Foot			1·25	
Thorax	0·85–0·90	0·87	41·3	19·4
Abdomen and pelvis	1·05	1·05		24·2

3. The range of movement of joints should permit all physiological movements and it should be possible to render the dummy quite flaccid or, alternatively, to apply tension to the joints so that conditions of rigidity of the body could be simulated, if necessary. The design range of joint movements is set out in Table II. In order to achieve spinal flexibility the dummy has six fibre-glass vertebrae in the cervical region and six in the lumbar region. The friction between these vertebrae can be adjusted by a tension cable within them. Some slight compromise with reality has been accepted in that the rib-cage zone is rigid, in order to allow a watertight instrument compartment to be built within it.

Table II.—*Design Range of Joint Movements*

Head relative to trunk	Flexion forward	60°
	,, backward	60°
	,, to either side	60°
	Rotation	85°
Arm at shoulder	Flexion	180°
	Extension	80°
	Abduction	145°
	Rotation	100°
Forearm at elbow	Flexion	145°
	Extension	2°
	Supination/pronation	180°
Hand at wrist	Flexion	90°
	Extension	60°
Thigh at hip	Flexion	145°
	Extension	45°
	Abduction	70°
	Adduction (cross legs)	45°
	Rotation	50°
Leg at knee	Flexion	145°
Foot at ankle	Flexion	75°
	Extension	45°
Spine	Forward	45°
Rib-cage and shoulders in relation to pelvis	Backward	30°
	Rotation	50°
Shoulders in relation to rib-cage ("clavicular movement")	Down	5°
	Up	35°
	Forwards	20°
	Backwards	20°

4. It was required that the various properties of the dummy should remain as constant as possible, despite storage and repeated exposure to fresh or salt water. Two methods of construction seemed possible. First, to use any convenient materials, whether resistant to sea-water or not, and then to encase the dummy in an impervious skin to protect its interior parts. The second method was to use for skeleton and flesh parts materials which are inherently resistant to sea-water and thus to dispense with the need to rely upon the integrity of an impermeable skin. The second method seemed more reliable, and was chosen. The appropriate skeletal member was carefully weighed and then placed in position in the appropriate mould. It was then encased in polyvinyl moulding-compound of a density calculated to achieve the correct mean density for the segment.

Results Achieved

The densities planned and the densities achieved for each body segment are set out in Table I. The range of joint movements specified in Table II has also been achieved.

In total volume and total mass the dummy is a little smaller than was planned, being 93% of the volume and mass of the 50-percentile man. In other words, the dummy is of the proportions of the 50-percentile man, but he is about 7% smaller. By design the dummy should have weighed 165 lb. (74.8 kg.) and should have displaced 151 lb. (68.5 kg.) of water when immersed to a depth of 60 in. (152 cm.). In fact, the dummy weighs 153 lb. (69.4 kg.) and displaces 140 lb. (63.5 kg.) of water when immersed to 60 in. (152 cm.). Table I also shows the percentage mass of the body segments to which the dummy was designed and the percentage masses of the dummy's actual body segments. These figures should be regarded with some reserve, because the dummy cannot be dismembered in precisely the planes used to define the body's segments. In particular, the dummy is necessarily so constructed that a segment of buttock remains attached to the trunk, which, in accordance with the plane used to define the division, would appertain

to the thigh. Thus the dummy's trunk mass appears somewhat increased and the thigh mass a little reduced.

The reasons why the dummy is a little smaller and lighter than the 50-percentile man are almost certainly two. First, the moulding compound used for flesh has to be poured into the moulds at high temperature. Some expansion of the skeleton would occur at these temperatures, so that the mould would not permit the entry of exactly the calculated volume of "flesh." Contraction of the skeleton and consequently also of the flesh moulding would occur on cooling. The second reason is that, because of the form of construction, all joints contain open cavities into which water can penetrate on immersion. Such cavities can hardly affect buoyancy, since on immersion they become filled with water which approximates to the density of the dummy, but they do appear as deficiencies of volume when this is measured by immersing the dummy in water. The loss of weight of the 50-percentile man as he is progressively immersed in fresh water up to the 60-in. (152-cm.) level has been calculated. The values have been reduced by the fraction 93/100, since it is known that the dummy is smaller in this proportion. These values are plotted as the continuous line in Fig. 3, in which the actual values obtained by progressively immersing the dummy are shown by dots. The volume centroid of the whole dummy is at 38½ in. (97.8 cm.) from the feet, and this agrees with the 50-percentile man.

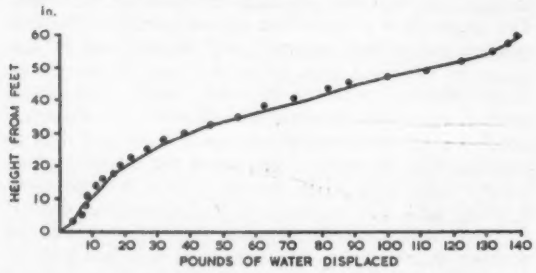


FIG. 3.—Weight loss of 50-percentile man as he is progressively immersed in fresh water.

Centres of Gravity of Segments.—The centre of gravity of each limb segment has been determined and related to the planes cited in W.A.D.C. Technical Report 55–159. The centres are, in all cases, within 2% of the correct positions. The centre of gravity of the whole dummy is 37½ in. (92.7 cm.) from the feet, and this conforms with the 50-percentile man. Fig. 2 shows the completed dummy.

Behaviour of the Dummy.—So far the dummy has been tested only in still fresh water. Without any extraneous buoyancy the dummy sinks, feet slightly first, in a manner reminiscent of the behaviour of the anaesthetized subject used by Macintosh and Pask.[3] When wearing a wartime R.A.F. Mae West the dummy floats in a 45-degrees face-upwards position, as did the anaesthetized man. When the dummy, wearing the Mae West, is deliberately placed face downwards and horizontal on the surface of the water, it rights itself by a combined tilting and twisting movement as did the anaesthetized man. Macintosh and Pask found that a particular buoyant suit which added buoyancy over all body segments caused the anaesthetized subject to float in a stable manner, either face up or face down, depending on how he was placed. The dummy behaves similarly.

Discussion

An attempt has been made to construct a dummy which resembles as closely as possible an inert man in those properties which may be expected to affect the position in which a man would float when supported by life-saving gear. If the dummy becomes accepted as a test-object it is hoped that the orientating properties of life-jackets may in future be determined in a more objective and less time-consuming manner than in the past. It is also hoped that the existence of such a test-object may enable marine architects more easily to study the problems of life-jacket design. The dummy is soon to be used for tests of life-preserving gear in real sea conditions.

If the dummy, representative of the 50-percentile man, becomes accepted it may be necessary to attempt to construct 5-percentile and 95-percentile dummies of men and perhaps also to study the problems involved in making dummies representative of women and children. The dummy may also be useful for the study of such physical problems as the vertical accelerations to which a man is subject when floating in various life-jackets, the rate of heat loss when various forms of protective clothing are used, and the rate of drift of castaways in various sea conditions. This dummy has been made as accurately as possible in accordance with the available data. It is uncertain how great a degree of accuracy is necessary in practice. Simpler and cheaper dummies can now be made and their performance compared with this prototype.

Summary

A dummy has been constructed which resembles an inert man in those properties which may be expected to influence floating in water. It is believed that the dummy will be useful in the design and testing of life-preserving gear.

The construction and dimensions of the dummy are described.

This project has been made possible by a generous grant from the Sir Halley Stewart Trust. Preliminary inquiries were supported by Messrs. P. Frankenstein & Sons Ltd. The dummy was constructed by the Sierra Engineering Corporation of California. Their generous interpretation of the terms of their contract has been most helpful. The dummies constructed by this firm are usually nicknamed "Sierra Sam," and this one, not surprisingly, is known as "Seaworthy Sierra Sam." The R.A.F. Institute of Aviation Medicine greatly assisted in the initial trials, and the Royal National Life-Boat Institution has made possible the sea trials at present in progress.

REFERENCES

[1] *Daily Telegraph and Morning Post*, July 25 and November 9, 1960, and March 21 and 30, 1961.
[2] International Conference on Safety of Life at Sea; Final Act. H.M.S.O., London. 1960.
[3] Macintosh, R. R., and Pask, E. A. *Brit. J. industr. Med.*, 1957, 14, 168.
[4] "Space Requirements of the Seated Operator." by W. T. Dempster. Wright Air Development Centre, 1955. W.A.D.C. Technical Report 55–159.

The Ministry of Health has sent a memorandum to Regional Hospital Boards, Hospital Management Committees, and Boards of Governors drawing the attention of hospital authorities to the need for employing more part-time nurses and midwives. The memorandum makes suggestions on the recruitment, reception, welfare, hours of duty, and refresher training of such part-time staff as well as for their introduction into the hospital life and work.

RADIOACTIVE FALL-OUT

On October 24 the Medical Research Council issued this statement on radioactive fall-out in the light of the resumption of nuclear weapon testing.

1. In December, 1960, the Medical Research Council published their second report *The Hazards to Man of Nuclear and Allied Radiations* (Cmnd. 1225), which included an assessment of the levels of exposure to radiation which had resulted from test explosions up to that time. The resumption of nuclear weapon testing in the atmosphere by the U.S.S.R. has, however, resulted in the further release of radioactive fission products, and, at the request of the Government, the Council have arranged to issue the following statement, which attempts to put in perspective some of the more important considerations that result from the new situation. A review of this subject would not have been possible without help from many people, and the Council would like to record in particular their indebtedness to the Agricultural Research Council and the United Kingdom Atomic Energy Authority, members of whose staff have provided valuable advice and assistance.

Mechanism of Deposition of Fall-out

2. Studies of the deposition of fall-out from weapons detonated during 1958 and in previous years have shown that the rate at which fission products pass from the stratosphere to the lower atmosphere and thence to the earth's surface varies greatly according to the size of the explosion and the height, latitude, and time of year at which it occurs. Deposition from large explosions has been found to be most rapid when debris is released into the lower stratosphere in high latitudes during the autumn.

Types and Sources of Radiation Exposure from Fall-out

3. *Short-lived Isotopes.*—The significance of tests involving substantial and rapid fall-out is that, soon after the tests, considerable quantities of short-lived radioisotopes, which will not have been retained in the stratosphere sufficiently long to decay to negligible levels of radioactivity, are likely to be deposited on the earth's surface. These short-lived components of fall-out contain both materials, such as Zirconium 95, which are not absorbed into the body but contribute to the external radiation received by the whole body, and materials which are absorbed into the body such as Iodine 131, which becomes concentrated in the thyroid gland. If present in sufficient amounts these short-lived materials may, in the short time during which they retain their radioactivity, give doses comparable to those delivered over much longer periods by the longer-lived materials produced in the same explosions.

4. *Long-lived Isotopes.*—The chief longer-lived components of fall-out which require consideration are Caesium 137, Carbon 14, and Strontium 90. Caesium 137 and Carbon 14 are of importance because they give rise to general irradiation of the body, including the gonads. The dose rate from Carbon 14 is very much lower than that from Caesium 137, but, as it will continue for very long periods, the total dose over hundreds of generations may be similar. Strontium 90, both because of its long half-life and because it becomes concentrated in bone, causing prolonged irradiation of bone and bone marrow, is still regarded as the most important single indicator of the possible total hazard to the individual.

Assessment of the Hazard from Fall-out Prior to the Present Tests

5. The Council's second report on *The Hazards to Man of Nuclear and Allied Radiations* (Cmnd. 1225), which assessed the possible extent of the hazard caused by test explosions up to the end of 1958, provides some background for considering the possible consequences of recent tests, and relevant parts of it are briefly reviewed below.

Genetic Effects

6. With regard to the genetic effect from all test explosions which had taken place up to the end of 1958, the Council concluded that the mutations which might be caused were likely to be few in relation to those produced by natural radiation: the latter are themselves believed to form one-tenth or less of the mutations newly arising in any generation.

Somatic Effects

7. As to effects on individuals, among the most important components in fall-out are Iodine 131 and Strontium 90. From the amounts of Iodine 131 observed in human thyroid glands, the Council concluded that the average thyroid dose delivered by this radioisotope as a result of nuclear explosions which had taken place prior to their 1960 report was unlikely to have exceeded one-quarter of the radiation received from natural sources during any year.

8. Investigations of Strontium 90 in human diet in the United Kingdom were commenced in 1955 and were considerably expanded in 1958. The contamination of milk receives particular attention because dairy produce contains most of the Strontium 90 which the population ingests. Samples of milk drawn from depots handling over 40% of total production are examined. Other foods are also sampled so that the average Strontium 90 content of diet throughout the country can be assessed.

9. Between 1958 and 1959 the ratio of Strontium 90 to calcium in average diet in the United Kingdom increased by 50%, but the recent Agricultural Research Council report (ARCRL 5) shows that in 1960 it decreased to little above the 1958 level. This decrease was due to the reduced rate of fall-out consequent on the cessation of testing, and reflected the fact that, when the radioactive fall-out was relatively high, the contamination of diet was due primarily to the direct entrapment of the recent deposit on growing vegetation. Strontium 90, however, also enters plants from the soil. This is a slower but continuing process, so that, even if fall-out ceased, diet would continue to be contaminated, though at a reduced level, for a considerable period.

10. The results of assays of human bone are now available for the five years 1956–60. In each year the highest concentration of Strontium 90 was found in children about 1 year old. In this age-group there was a progressive but slow rise each year until 1958, a doubling of the 1958 value during 1959, but a fall in 1960 which has continued in 1961. The average value in these infants of 4 strontium units—that is, 4 micromicrocuries per gramme of calcium—at the peak in 1959 was some 1/16th of the value (67 strontium units) regarded by the Council as the maximum permissible average value in the whole population.

11. Children born in the year 1955 have been exposed to Strontium 90 from their diet over their whole lifetime.

Although in 1956 the average value in their bones was one strontium unit, the value in 1960 was only fractionally greater (1.4 units). Older children have formed only part of their bone structure from contaminated food, and the bones of those born between 1945–50 showed only one strontium unit in 1960.

Estimation of Additional Exposure due to Recent Atmospheric Tests

Fall-out Resulting from Recent Tests up to the Middle of October, 1961

12. The recent tests by the U.S.S.R. are reported to have included explosions both in the kiloton and the megaton range and to have occurred in Central Siberia and the Arctic. As would have been expected from experience in 1958, the radioactivity reaching the ground in recent weeks as a result of the present series of explosions has come mainly from short-lived components which are deposited within a few weeks of the explosion. The deposition of longer-lived components, such as Strontium 90 and Caesium 137, is likely to be greatest next spring.

Radiation Exposure from Short-lived Isotopes

13. Since Iodine 131 is the main short-lived isotope absorbed into the body, extensive measurements are being made of levels of Iodine 131 contamination following the present series of tests. Early results of the survey, which is being carried out by the Agricultural Research Council, are given in the Appendix.

14. It is estimated that the average radiation exposure to the thyroid from this isotope in the fall-out already measured in the United Kingdom from the present tests is likely to be less than the figure of one-quarter of the radiation received from natural sources during any year referred to in paragraph 7 above. However, the value for infants in their first year of life may now approximate to that received annually from exposure to natural sources.

15. Because Iodine 131 is taken into the body predominantly through milk, the Medical Research Council have had under review the maximum sustained level in milk which might be regarded as allowable. They have based their recommendations on similar criteria to those used in setting the dose-levels permissible in the general population from Strontium 90. They have concluded that an acceptable dose would not be exceeded in any age group of the population unless an average concentration of Iodine 131 in milk of 130 micromicrocuries per litre was exceeded over a period of one year, or higher concentrations for correspondingly shorter times. The level has been set to provide a margin of safety for the section of the population in the group in which the dose rate would be highest—namely, infants up to the age of 1 year; considerably lower radiation doses would be received by older children and adults consuming the same milk. Allowance has also been made for the likely variation in the concentration of radioiodine in local milk supplies. The dose referred to will not be reached unless present levels of Iodine 131 continue for several months as a result of further weapon tests or are substantially increased. A marked decrease may be expected within a few weeks of the cessation of tests.

Radiation Exposure from Long-lived Isotopes

16. As the highest fall-out rate of some of the longer-lived radioactive substances, such as Strontium 90, may be expected in the late spring of 1962, it is not yet possible to predict the total additional radiation dose to which the population has been committed by the recent tests. However, as the levels of radioactivity measured in air have been similar to those observed at an equivalent time after explosions in the autumn of 1958, there is at present no reason to believe that tests from which fall-out has so far been detected will involve an additional radiation exposure from external radiation or from Strontium 90 which differs greatly from what has been experienced hitherto. It may be concluded that Strontium 90 from tests so far carried out will not give rise to bone levels approaching those which the Council laid down in their report of December, 1960, as the maximum permissible in the general population.

Radiation Exposure from Inhalation of Radioactive Materials

17. Consideration has also been given to the inhalation of radioactive materials, including Plutonium. It has been concluded that the extent of radiation exposure from such sources is unlikely to be comparable in importance with that from the other sources mentioned.

Radiation Exposure from Underground Tests

18. The Council are informed that it is not expected that underground tests, such as the United States has been carrying out, will contribute to world-wide contamination.

Possible Consequences of the Explosion of a Fifty-megaton Bomb

19. It appears likely that the explosion of a 50-megaton bomb during the present series of tests would cause the total energy released from this series to correspond approximately with that of explosions occurring in the two years 1957–8 (according to the Ministry of Defence statement of May 5, 1959). If the bomb is exploded in the atmosphere the resulting fall-out will depend on the extent to which the energy is due to fusion rather than fission and on the altitude and site of the explosion.

20. The explosion of such a bomb in the atmosphere in northern latitudes during the autumn could be followed by considerable fall-out of shorter-lived radioisotopes. Radioiodine deposition due to the series might then be substantially greater than that from previous tests and the contamination of milk in the subsequent weeks might cause the annual mean level to approach that specified in paragraph 15 above.

21. Radioisotopes of medium half-lives, such as Zirconium 95, might be expected to raise the external radiation level in the open for some months by an amount comparable with the dose rate received from natural sources.

22. It is not yet possible to predict with any accuracy the total additional radiation dose to which the population will be committed by the current series of Russian tests, including the explosion of a 50-megaton bomb. Bone concentrations of Strontium 90 in young children might rise in the course of one year to about twice the maximum level observed hitherto, but the level regarded as the maximum permissible one by the Medical Research Council would not be reached.

Arrangements for Monitoring and Assessing the Fall-out Situation

23. Regular measurements of radioactivity in rain, drinking-water, food including milk, air, soil, vegetation, and human bone are continuing according to a country-

wide programme under the supervision of the Medical Research Council and the Agricultural Research Council. The results of measurement of radioactive fall-out are published at frequent intervals. Premature attempts to interpret the significance of individual early measurements directly in terms of human hazard can be extremely misleading. Variations in the measurements are to be expected, both from day to day and as between one place and another. The significant factors are average levels over long periods of time.

24. The situation with regard to fall-out and the hazards from it is kept under close and continuous review, and the bodies responsible for so doing have undertaken immediately to inform the Government if there should be any major change in their assessments.

APPENDIX

Measurements of Iodine 131 in Milk

When it became apparent that the new series of nuclear explosions might lead to appreciable quantities of Iodine 131 in milk, the Agricultural Research Council Radiobiological Laboratory commenced an examination of milk from eight depots or farms located in Central and Southern England, Wales, Scotland, and Northern Ireland. The samples are analysed frequently, usually daily. The mean results so far obtained are shown in Table I.

TABLE I

Week Commencing	μμc Iodine 131/litre
September 16, 1961	85
,, 24, 1961	109
October 1, 1961	138
,, 8, 1961	150
Mean for four weeks	120

Levels of Iodine 131 in milk produced at 8 sites in different parts of the country.

In the first few days of the week commencing October 15, 1961, the average level fell to below 100, but those results which are now available for the latter part of that week indicate a return to the levels observed 10 days previously.

More detailed investigations of the general level of milk throughout the country were made for October 1 and 15, 1961. On these dates representative samples were obtained from depots which together handle over 40% of the total milk produced in each of 10 zones into which the whole country has been divided. The statistical organization of this elaborate scheme, which is also in operation for Strontium 90, has been described in reports by the Laboratory. The average results for the two sampling occasions are shown in Table II.

TABLE II

Zone	μμc Iodine 131/litre
1. Northern England	103
2. North-West England	92
3. East and East Midland	71
4. West Midland	100
5. Wales	153
6. South and South-East England	102
7. Mid-Western England	86
8. Far Western England	105
9. Scotland	190
10. Northern Ireland	165
Country-wide mean weighted for production	113

Levels of Iodine 131 in milk produced throughout the United Kingdom—mean of values for October 2 and 16, 1961.

The means shown in the two Tables are in close agreement, and the significance of the figures is discussed in the foregoing statement.

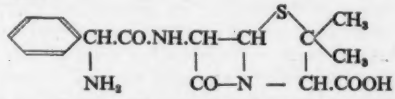
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Ampicillin

"Penbritin" (Beecham Research Laboratories).

Chemistry.—Ampicillin is a new synthetic penicillin prepared from 6-aminopenicillanic acid. It is 6[D(−)α-aminophenylacetamido]penicillanic acid and has the structural formula



In contrast to benzylpenicillin (penicillin G) it is relatively insoluble in water (about 10% at room temperature), but it is about equally stable. It is issued in capsules containing 250 mg. of active material.

Pharmacology.—Ampicillin is relatively acid-stable and is active when given by mouth. It has a much wider range of activity than benzylpenicillin, but it is destroyed by penicillinase and is therefore ineffective against most penicillin-resistant staphylococci. Other strains of staphylococci, as well as haemolytic streptococci, *Str. faecalis*, and pneumococci, are approximately as sensitive to it as to benzylpenicillin. Its distinctive property is its much greater activity against Gram-negative organisms and in particular against salmonellae, *Escherichia coli*, shigellae, and *Haemophilus influenzae*. Some strains of *Proteus* are sensitive and some resistant, while *Pseudomonas pyocyanea* and *Klebsiella aerogenes* are resistant. Ampicillin is bactericidal in contrast to the other wide-spectrum antibiotics, which are bacteriostatic. It is fairly slowly absorbed and excreted when given by mouth, and a peak concentration is reached at about 2 hours; significant blood concentrations are still present at 6 hours. About a third of a dose is excreted unchanged in the urine. A high concentration is reached in bile.

Therapy.—Dosage depends on the nature and severity of the infection. For infections due to Gram-positive organisms 250 mg. six-hourly is recommended. For infections with Gram-negative organisms between 1.5 and 2.25 g. over each 24 hours should be given in divided doses, though with urinary-tract infections 250 mg. six-hourly should usually be adequate, since the drug is concentrated in the urine. The dose should be doubled if the organisms are relatively insensitive. At the time of writing ampicillin has been shown to be effective against infections of the urinary tract, but relatively ineffective against infections of the bowel. It seems probable that it will be active against infections which respond well to benzylpenicillin. Unfortunately clinical evidence is lacking on its efficacy in the treatment of biliary-tract infections, systemic Gram-negative infections, and conditions such as enteric fever and brucellosis which, though rare in Great Britain, are of great importance in other parts of the world.

Though ampicillin is a most interesting and promising antibiotic it cannot be said that at present either its greater effectiveness or its lessened toxicity over other available remedies has been adequately demonstrated. G. T. Stewart and his colleagues[1] state that "it cannot at present be recommended for the treatment of intestinal carriers of salmonellae." The practitioner would be well advised to proceed cautiously with the use of this new antibiotic until more evidence of its activity in clinical practice and its toxicity has been published and critically evaluated.

Side-effects.—Of 18 reported patients who have received ampicillin three developed urticarial rashes and three infants had loose stools. *Candida* appeared in several cases.

N.H.S. Basic Price.—100 capsules, £15 6s. 8d.

REFERENCE

[1] Stewart, G. T., *et al.*, *Brit. med. J.*, 1961, 2, 200.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Oral Poliomyelitis Vaccine

Sir,—Your leading article (October 21, p. 1072) fails to make proper distinction between the use of oral poliomyelitis vaccine for general immunization and for the control of epidemics. In general use the objective is to immunize susceptibles. In an epidemic situation, however, it may be too late to achieve this goal of individual protection whatever vaccine is used, unless the epidemic is protracted. The alternative approach which offers hope of more immediate effect, particularly in an explosive outbreak, is to attempt to break the chain of transmission of infection by mass feeding of oral vaccine. Alimentary infection by the attenuated virus present in the vaccine should then interfere with the spread of wild virus circulating in the community. For this purpose the choice favours that strain of virus which will most readily establish itself in the gut under all circumstances. The Sabin type 2 strain is certainly much more effective in this respect than the Sabin type 1 strain, particularly in those who have previously received Salk vaccine. It would therefore be expected to exhibit a greater interfering effect on the spread of infection than would the type 1 strain.

The control of outbreaks of poliomyelitis by means of mass use of oral vaccine has so far been attempted on only half a dozen occasions. In most of these it has been claimed that the outbreak has been halted, but only in the Singapore epidemic have the results proved susceptible to statistical analysis. This showed evidence of protection in children given type 2 Sabin vaccine during a type 1 epidemic.[1 2] In two of the instances of the use of vaccine at a time when cases of paralytic disease were occurring in the community, controversy has developed concerning the cause of the illnesses subsequent to the administration. These were in Dade County, Florida,[3] and in West Berlin.[4] In the latter city the experience of cases of neurological disorder in vaccinated persons threw doubt on the safety of the vaccine and has probably influenced public health policy in West Germany. Nevertheless no certain proof has or can be adduced in either of these outbreaks that the vaccine was to blame, nor can it be exonerated, largely because in both instances the vaccine contained the same type of virus as that causing the outbreak.

One of the aims of public health is surely the assessment of the measures taken to interrupt the course of nature. It is most necessary to be able to interpret the course of events during mass use of poliovaccine. In our view it is hardly possible to do this with any precision if the vaccine strain used cannot be distinguished in the laboratory from the virus causing the outbreak. To add two more virus types to the one spreading in the community as you have urged savours of the witches' cauldron rather than of scientific endeavour. The use of Sabin type 2 vaccine in Hull is, however, supported both by practical experience and by theoretical considerations.

On entirely different grounds, the comment in your leading article concerning the use of this vaccine in Hull by the Ministry of Health appears to us to be most untimely. Publicity was given to the opinion that the wrong sort of vaccine was being used at the very time when the majority of the citizens of Hull had either just received or were about to receive it. The fear of poliomyelitis, though out of proportion to the true significance of the disease, is a very potent force in modern society. Your leading article can only have increased alarm and made the task of the Health Department more difficult.

—We are, etc.,

C. H. Stuart-Harris.
John Knowelden.

Departments of Medicine
and of Preventive Medicine and Public Health
University of Sheffield.

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Sir,—We would like to question the validity of many of the statements and inferences made in the discussion, summary, and conclusions of the Report of the P.H.L.S. laboratory trial of living attenuated poliovaccine (October 21, p. 1037) and in your leading article (p. 1072).

It is claimed that the antibody level achieved with Sabin vaccine is of the same order as that following three doses of Salk vaccine. Any comparison of antibody levels must be related to the titre and potency of vaccine used and to the group of people who were immunized. In the P.H.L.S. trial ten times as much virus was fed as in most other trials, and the group of children studied were infants mostly from single-child families. The infants were selected to reduce the possibility of natural infection with wild enteroviruses. We think it entirely wrong to conclude that similar results would be obtained with 10^5 instead of 10^6 $T.C.D._{50}$ and in the general child-population as opposed to a specially selected group. The reason for this is that in the absence of siblings the vaccinated infants would be less likely to be carrying interfering viruses. Enteroviruses may be carried by 10 to 20% of the child population in parts of the United Kingdom. (It seems reasonable to assume that if oral vaccines are used on a large scale a dose of 10^5 $T.C.D._{50}$ is likely to be used rather than 10^6 $T.C.D._{50}$ because the bulk of evidence for safety is based on experience with the smaller dose.)

We consider that the type of study done by the P.H.L.S. in which there was little contact between vaccinees is of more value in assessing the vaccine's potentialities for a continuing immunization programme than those studies which have depended in part for their results on the infectious properties of the vaccine viruses.

It is stated in the P.H.L.S. report that the factor of safety of Sabin vaccines may be neglected. The P.H.L.S. study, because of the small numbers involved, could by itself give little indication of the safety of oral vaccines. The evaluation of the safety to the recipients is comparatively easy and can follow the usually accepted lines. It should be pointed out that

in the past you have questioned the acceptability of Russian methods of surveillance.[1] The community safety of an infectious virus vaccine has raised, and continues to raise, most difficult problems. To some extent these can be overcome by mass area vaccination as recommended by the Russian and Czechoslovakian workers. We consider that more definite knowledge of the safety of the vaccines when used for day-to-day immunization is desirable before these vaccines are considered as a replacement for the Salk vaccine in the United Kingdom. The P.H.L.S. study does not report any attempt at community surveillance. We do not pretend that this type of surveillance would have been easy. But would it have been possible, for example, to make some sort of comparison between the incidence of paralytic poliomyelitis since the trial, in those areas where vaccine was fed, and in comparable areas where vaccine was not fed?

Trials of living oral vaccines which have not been followed up by mass immunization programmes have in certain places been followed by epidemics the next year. Obviously this was likely to be coincidental, but can we be sure? There are theoretical reasons why surveillance should not be confined to the period immediately following the trial. The problem of community safety is a difficult and complex one and has been the major factor in preventing earlier trials of oral vaccines in Western countries.

We consider both the P.H.L.S. report and your leading article treat the problem of the community protective effect of the two types of vaccine (oral and inactivated) in rather a superficial manner. We have pointed out the difficulties inherent in the interpretation of experimental studies.[2] The comparative resistance of the intestine to reinfection with large doses of attenuated virus is certainly in favour of the oral vaccines, but it may be beside the point. If the immunity conferred by Salk vaccine reduces the chances of virulent polioviruses establishing themselves in the pharynx, may not this be all that is required? We know of no conclusive evidence that pharyngeal virus does not play a major part in the extra-familial spread of epidemic strains of poliomyelitis. As we have stated before,[2] we think that the influence of both vaccines on the community spread of virulent viruses will be apparent from broad epidemiological studies. The case that Salk vaccination is having a profound community (herd) protective effect in the U.S.A. is argued by Bodian in a recent paper,[3] and the development of a herd immunity is one interpretation which can be put on the virtual disappearance of poliomyelitis and poliovirus from Sweden.[4] Is there supporting data from the United Kingdom? It might be interesting to compare the attack rates in different areas in relation to the vaccination status of the population, particularly of the young children.

We think it unfortunate that in the discussion of the P.H.L.S. report references to poliomyelitis in the U.S.A. and in Canada fail to take into account the larger differences in immunization rates in different areas, the potency of the vaccines used, and the overall incidence of the disease in 1960 and 1961. In the same discussion it is stated that to ensure a herd immunity 80 to 90% or even higher of the susceptible population have to be vaccinated. We would suggest that 80 or 90% of the child population would probably have to be vaccinated with either oral or inactivated vaccines to achieve a herd immunity. The dominant role of young children in the dissemination of the infection is now fairly widely accepted, and it is extremely doubtful whether the suggestion of immunizing 90% of the entire population under 50 years is at all necessary.

Both the P.H.L.S. report and your leading article emphasize the comparative ease with which oral vaccines can be administered. Most advocates of inactivated vaccines would consider that potent quadruple vaccine (containing poliomyelitis, diphtheria, whooping-cough, and tetanus antigens) was at least as easy to administer in a continuing immunization programme.

Your leading article refers to the successful use of trivalent oral vaccine in Tashkent in 1959 during an epidemic of type I virus. We consider this gives an altogether erroneous impression of what happened in Tashkent.[5,6] Despite the fact that nearly all children in Tashkent were fed vaccine, more than twice as many cases occurred after vaccination as before vaccination. The Russian workers were guarded in their claims of the effectiveness of this attempt at epidemic control, and Chumakov[5] stated that "it may be inferred that vaccination during an epidemic outbreak at least does not aggravate the situation, does not increase the frequency and severity of poliomyelitis cases." The one certain conclusion which can be drawn from the Tashkent experience is that epidemic control by means of oral vaccines is a relatively inefficient method of preventing poliomyelitis.

Your leading article says that the views expressed in the P.H.L.S. report should encourage the Ministry of Health to change over as soon as possible from Salk to Sabin vaccine for general immunization. (When comparing the vaccines it must be remembered that the term Salk vaccine has been used to describe a number of products of very different potencies.) Any decision to change must rest on unequivocal evidence that Sabin vaccine is as safe and as effective. We should compare what *could* be achieved with Salk vaccine (not what has been achieved) with what could be achieved with oral vaccine. In some ways it has been difficult to understand the United Kingdom policy with regard to Salk vaccine over the past few years. Sweden, for example, has been using a more potent Salk vaccine which appears to give virtually complete protection even after the second dose. We consider that, if the Ministry of Health had shown a little more flexibility in its manufacturing requirements and had perhaps been prepared to pay a little more for the vaccine, British manufacturers could have made as good a vaccine as the Swedes. In our opinion the difference in the effectiveness between the Swedish and British vaccine was predictable.

It should be pointed out that there is no evidence to suggest that yearly injections are necessary when potent Salk vaccine is used. The high antibody titres which can be achieved with potent inactivated vaccines suggest that they might give a more durable immunity than that conferred by oral vaccines. We wonder why the development of a quadruple vaccine (poliomyelitis, diphtheria, tetanus, and whooping-cough) which has been used extensively in Canada and the U.S.A. was not considered as an urgent problem in the United Kingdom. The enormous benefits of such a vaccine to children, parents, and public health authorities alike have been apparent for some time.

The shortcomings of Salk vaccine as used in the United Kingdom can be explained not only by low

potency but also by "under-utilization." We do not think that "under-utilization" of vaccine has been entirely due to public apathy, since adequate coverage of the important age-groups has been obtained in some areas. Has there been a failure to appreciate the need to achieve high rates of immunization in pre-school children?

No mention is made in your leading article of the incidence of poliomyelitis this year in the U.S.S.R. or in the U.S.A. Surely this must be one of the factors carrying most weight in any decisions on future policy. In the U.S.S.R. up to the end of 1960 92% of the population up to 20 years of age had been vaccinated with all three types of live poliovirus vaccine.[7] There were also plans to revaccinate this population in 1961.[8] At the Seventh Symposium of the European Association against Poliomyelitis held in Oxford last month (see *Journal*, October 7, p. 951), Soloviev reported that during the first six months of 1961 there had been 1,572 cases of poliomyelitis in the U.S.S.R. (provisional figures). Comparable figures from the United States show that, while by the autumn of 1960 about 75% of the same age-group have received three or more injections of Salk vaccine, the total number of all poliomyelitis cases for the first six months of 1961 was only 237. The number of cases in the United States has remained at a low level since June. We would certainly not recommend reading too deep a significance into the figures for just one year, but surely they merit some consideration? Does this failure to eliminate poliomyelitis from the U.S.S.R. indicate a lack of effectiveness, or a lack of safety of oral vaccines, or both?

It is now known that the vaccine used in the P.H.L.S. trial would fail to meet present-day requirements of purity. If oral vaccines are to be used in the United Kingdom as recommended in your leading article, it is to be hoped that the standards of purity, uniformity, and antigenicity required will be at least as high as those required in the United States of America, and that the principle of gradual introduction will be adhered to both for individual batches and for the product as a whole.—We are, etc.,

G. W. A. Dick.
D. S. Dane.

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Belfast.

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Nationalities of Junior Staff

Sir,—Being very much concerned with the post-graduate education in surgery of men from overseas, I was very interested in the article from the Sheffield Regional Hospital Board (October 7, p. 950). Whilst many of these men are very good indeed, it is possible to have too much of a good thing and in some hospitals the preponderance of overseas doctors could be a source of difficulty. For example, half the hospitals with junior staff of five and under had no one at all from the British Isles (see Table II). Similarly, well over half the "housemen" in the region were recruited from overseas (Table I). These two parallel sets of observations could very well be a matter of concern to the Minister of Health, but the responsibility carried by these doctors is much less than that carried by the registrars and particularly the surgical registrars. It is to this latter group that I want especially to direct attention.

There were roughly five overseas registrar appointments to every two from the British Isles (Table IV). Since the overseas men had a higher "wastage" rate, the proportion of those in service was probably about two to one. In general surgery, orthopaedics, and casualty, however, the overall numbers, including housemen, was three to one, as against a fifty-fifty break in medicine, gynaecology, and obstetrics. It is a fair assumption therefore that three out of four surgical registrars in the regional board hospitals were recruited from overseas and that the great majority of registrars in the smaller, most isolated, peripheral hospitals were Asians. This cannot be regarded as satisfactory since these men, often working by themselves, are frequently called upon to shoulder responsibilities for which they are (through no fault of their own) untrained and unfitted.

In would be interesting to have comparable figures for registrars *and* senior registrars for the Sheffield teaching hospitals. It is a fair guess that these would show a complementary picture, with a preponderance of British graduates. These, paradoxically, educated in our own environment, relatively well trained, and at least understanding fully and fluently speaking our language, are to be found in the hospitals where they receive most supervision and act mostly as assistants. If we could strike an average for the combined, teaching and regional, surgical registrars *and* senior registrars we should probably get in the region of an even fifty-fifty break. This, having regard to our desire to retain an education link with overseas territories, would, I suggest, be an acceptable division of labour, *provided the spread was reasonably even, that the least experienced were under tutelage, and that the best qualified to discharge it were given the greatest responsibility.*

This desirable state of affairs can never come about so long as individual hospitals are in competition for the best candidates. These will naturally go to the more attractive hospitals, as they do now, with the deplorable results the Sheffield workers have described. There is one, and I believe only one, solution which is, I am informed, administratively acceptable. It is to recruit all registrars and senior registrars to one regional-cum-teaching hospital service pool. At regular quarterly or half-yearly intervals an appropriate committee could then meet to arrange postings by rotation, in accordance, so far as possible, with three desirable objectives,

namely: (1) The educational interests of these trainee surgeons; (2) the staffing needs of the hospitals; and (3) the wishes of the men themselves.

Such a system would involve the surrender of some part of the right of appointment at present enjoyed by the management committees, but the greatest good of the greatest number would be served, and would be seen to be served, and any strong personal feelings could always be expressed and given whatever weight they seemed to merit. In general, one would envisage the beginner starting in the teaching and "para-teaching" hospitals, graduating to greater responsibility in an intermediate group, and later, when experienced, to the most peripheral units. Finally, a man would go to a special unit or back to a teaching centre for "finishing" prior to consultant appointment.

These changes will not be brought about except through the efforts of those who think them worth while. I sincerely hope that any who see merit in these suggestions will say so in no uncertain fashion. Their implementation will call for strong backing from several sides of the profession.—I am, etc.,

Department of Surgery,
The University of Liverpool. CHARLES WELLS.

Record of Antitetanus Immunization

SIR,—In his letter (October 14, p. 1020) Mr. William Gissane has raised an important question: How to tell at once whether an injured child has been actively immunized against tetanus? Valuable as record cards of immunization may be, they will generally fail in this purpose, because children will seldom carry them in their pocket. Tetanus is the only disease about which a child's immunological status must be known immediately. I can see no way of providing this information except by a tattoo mark.

After Mr. Norman Lake wrote an article on "Tattooing in the Service of Surgery,"[1] he kindly made at my request a small instrument, no bigger than a fountain pen, for imprinting through a drop of sterile India ink a small T on the skin. After trying various sites, I reached the conclusion that the best place for the tattoo mark was one situated an inch (2.5 cm.) below the crest of the ilium midway between the symphysis pubis and the sacrum. In this position it is habitually covered, even by the most tenuous of bathing costumes, but is readily exposed to view. The mark can be made after the primary series of injections with tetanus toxoid has been completed. The operation itself takes only a few seconds; it is painless; and the resulting mark is indelible. The needles can be rapidly sterilized by flaming alcohol. Messrs. Allen and Hanbury made me a slightly modified instrument which, if mass-produced, would probably cost no more than a guinea.

There is nothing new about tattooing. Parents do not usually object to having their children tattooed with vaccine lymph for smallpox or with B.C.G. for tuberculosis, even though a permanent, and sometimes unsightly, scar is left on the arm. Why, then, should they object to a neat little T on a spot that is normally hidden from view? Surely such a mark is a small price to pay for so great a benefit.—I am, etc.,

Public Health Laboratory Service,
London W.1. G. S. WILSON.

REFERENCE

[1] Lake, N. C., *Brit. med. J.*, 1958, **1**, 1084.

SIR,—With the future more widespread use of the recommended schedules for immunization (September 16, p. 763), a new generation should soon be growing up who are actively immune to tetanus. Unless adequate records of the injections are kept, and proper reference made to them, much of the benefit will be wasted and potential tragedies such as that described by Mr. W. Gissane (October 14, p. 1020) will continue to occur.

The family doctor is in the best position to be responsible for the immunization state of his patients. Any procedures performed by others should be notified to him by hospitals, welfare clinics, Services, etc., and he should provide his patients with personal record cards. Hospital staffs could then refer to him in cases of doubt where the personal-record system breaks down. Even a delay of 12–24 hours would be preferable to a serious error in procedure. Executive councils could help trace the young patient's family doctor, and if all else failed there need surely be no necessity to hold the patient in hospital if he were given a strongly worded letter to the parent requesting urgent attendance at hospital or surgery, and stressing the importance of immunization against tetanus.—I am, etc.,

Birmingham 5. DAVID SANDILANDS.

Routine Immunization

SIR,—Am I alone in reacting unfavourably to Ministry of Health Circular E.C.N. 379, dated September 12, which is I presume in the hands of all G.P.s in the N.H.S.? Dealing with the immunization of young children to diphtheria, the circular states: ". . . the Minister is advised that this prophylactic [FT] is no longer to be regarded as suitable for the primary immunization of children against diphtheria except in combination with an adjuvant."

Ministry of Health circulars in 1957 drew attention to the risk of poliomyelitis related to the use of alum-precipitated antigens, and recommended that such material *should not be used*. Further, the use of single as against combined antigens was forcefully suggested, and it was emphasized that *only* FT and TAF were supplied through the Public Health Service. It has I believe been universally accepted that FT is the safest and most suitable antigen for small (under 8) children. (I am of course writing only of cases where for many different reasons one is not proposing to give a combined antigen.) Now, apparently, FT is "out"—just like that. We are not told what is "in," but it is presumably one of the antigens formerly to be eschewed: are APT or PTAP to be applied after all by the Public Health Service?

I have sought the advice of my area M.O.H. on the best single diphtheria antigen for the young child, and he firmly recommended FT.

Some of us try to take an intelligent and responsible interest in deciding what material to use, but it might almost seem to the cynic that the toss of a coin would serve the purpose. I do not question the competence of the Minister's advisers, but to chuck at the G.P. a complete reversal of previous (and most unequivocal) advice without explanation, discussion, or suggested alternatives smells of deplorable public relations. And this is not an isolated example: the information about availability of a fourth polio injection reached G.P.s some weeks after its public dissemination on the telly.—I am, etc.,

Leatherhead, Surrey. ALAN N. COWAN.

Tetanus Prophylaxis and the Courts

SIR,—In the recent correspondence on tetanus prophylaxis it has not been mentioned that, as a result of the attitude of the courts (see October 14, p. 1021), it is a rule in some hospitals that casualty officers must give antitetanus serum in all relevant cases, even if the patient or parent offers convincing evidence of adequate immunization against tetanus.—I am, etc.,

East Malling, Kent. N. NAUNTON DAVIES.

Reprints

SIR,—Complaints have occasionally occurred in your pages from those who seek (however unwisely or unsuccessfully) to add to human knowledge by publishing their research work. They have complained of the expense of providing reprints to all who ask for them, especially when the request, usually from foreign parts, takes the form of a printed postcard which has the appearance of emanating from a library clerk rather than a genuinely interested colleague.

I suggest that we should free ourselves and our secretaries from this burden and at the same time make a contribution to the funds of British journals. Let you, Sir, and your fellow editors work out the cost of reprinting and posting our work and providing your journals with a reasonable profit. You keep the reprints, send them to those who want them, and charge them for the service. All we have to do is to post to you occasional batches of little buff postcards. You would be rendering a service indeed by dealing with them.—I am, etc.,

London W.1. RAYMOND GREENE.

Oral Leucoplakia

SIR,—I enjoyed reading your instructive leading article on oral leucoplakia (September 30, p. 877). You mention lichen planus in the differential diagnosis, and indeed this is becoming a common cause of white patches in the mouth. Apart from the series reported by Cooke,[1] we[2] described 45 cases presenting as a mouth disorder which had been collected for eight years up to 1957. Since then we have seen another 20 to 25 patients with this condition. An important point in connexion with these cases is that well over half develop superficial ulcerations, often recurring on the same site, and often associated with some local trauma from dentures or teeth.

In 1960[3] I reported that, of the 45 cases, four had later developed an epithelioma and two thickened white patches with histological characteristics of leucoplakia. In nearly every case this occurred at the site of repeated ulceration. Since this time two more cases of epithelioma associated with oral lichen planus have been seen, one on the lip and one on the buccal mucous membrane, and one of the cases previously reported as having leucoplakia developed an epithelioma. It thus appears that, in about one in ten cases of lichen planus presenting in the mouth, epithelioma or leucoplakia has developed. It is difficult to know how this can be avoided, but the least that can be done in cases of oral lichen planus, particularly with recurrent ulceration, is to reduce trauma and irritation from dentures, sharp teeth, and smoking.—I am, etc.,

Bristol. ROBERT P. WARIN.

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Orange-bolus Obstructions

SIR,—Undigested orange may cause symptoms or signs other than those of obstruction. A 73-year-old man presented at out-patients with a three-months history of anorexia, nausea, and upper abdominal discomfort amounting to pain at times. He lost weight rapidly over two months but gained weight when his general practitioner put him on a liquid diet with supplementary "complan." A barium meal (see illustration) showed a series of constant filling defects on the greater curvature

of the stomach. The man was admitted for laparotomy with a radiological diagnosis of carcinoma of stomach.

At operation four large undigested segments of orange were found embedded along the greater curvature of the stomach. These segments had to be dissected free from the otherwise normal gastric mucosa. There has been no recurrence of symptoms following laparotomy. The patient was able to recall eating a very dry orange and swallowing several segments whole about the time his symptoms first appeared.—We are, etc.,

Queen Elizabeth Hospital, Birmingham 15. P. R. KNIGHT. P. J. SCOTT.

Intramuscular Injections

SIR,—The tragic death of my old chief Professor Lambert Rogers stimulates me to reinforce his cogent arguments in favour of the vastus externus muscle as the site of choice for intramuscular injections. During the past 19 years, following his teaching and that of the late Professor Grey Turner, I have insisted upon the use of this site, and to the best of my knowledge there has been no untoward consequence.

Surely the buttock with its covering of potentially contaminated skin, its content of large vessels and nerves (the sciatic nerve being the largest in the body), and its vague boundaries (October 7, p. 956) is an unsafe reservoir for the deposition of drugs. I have personal experience of sciatic neuropathy, gluteal aneurysm, and numerous buttock abscesses, but the most tragic result of the choice of this site concerns a young man of 23 who was given slow-acting adrenaline for the relief of

asthma into the gluteal region. A massive clostridial myositis ensued, and, in spite of vigorous resuscitative and heroic surgical measures, he died. Although it is now more generally realized that muscle is a dangerous tissue for the deposition of adrenaline, death might have been avoided by the choice of a more favourable site.

Surely, Sir, it is time that those responsible for the training of nurses, and who still favour the traditional gluteal site for intramuscular injections, should reconsider their advice.—I am, etc.,

Newport, Mon. R. D. RICHARDS.

SIR,—May I also support the use of the vastus lateralis as a better site for intramuscular injections than the gluteal region, as advocated long ago by Professor Grey Turner? This is also favoured, I believe, by the medical defence societies, and the number of cases, known and unknown, of complications from injections in the gluteal region must now be very great. Like the late Professor Lambert Rogers (October 7, p. 956) I have never seen the haematoma mentioned in your annotation (September 16, p. 758), though admittedly infection has sometimes occurred, especially when irritating substances such as magnesium sulphate or paraldehyde in oil have been used, or when injection has been given too near the greater trochanter; and certainly infection beneath the fascia lata can be very troublesome. This, however, is rather a result of the present wave of hospital infection than a special risk of injections in this site.

A troublesome complication of gluteal injections of iron is the ugly staining of the skin which often results, as injection there is more likely than in the thigh to be subcutaneous than intramuscular owing to the great thickness of fat, and this is important again, now that administration of iron by this route is perhaps finding its rightful place after the scare of a little while ago. Some time ago Messrs. Reckitt and Sons (40 Bedford Square, London W.C.1) prepared for me at this hospital a coloured film-strip for instruction showing a suitable technique for injections into the vastus lateralis, and this may be obtained from them for showing to nurses and others.—I am, etc.,

Middlesbrough Maternity Hospital, Middlesbrough, Yorks. BRYAN WILLIAMS.

Geriatric Services

SIR,—Dr. Vera E. Claxton (October 14, p. 1020) is right in claiming that the geriatric problem is indeed urgent. While it is clear that in many areas more geriatric hospital beds and places in welfare homes are required, insufficient attention has been paid to the fact that a small increase in beds allocated to geriatric departments will, if properly used, produce a disproportionately great improvement of the over-all problem. By doing so, not only the general practitioner but many hospital departments are eased. This being so, it is a pity that administrators at regional board and management committee levels do not give more attention to increasing the facilities of their geriatric departments, even if at first this has to be at the expense of more ambitious schemes to expand other services. Unless some such help is given, acute wards will be completely bogged down by elderly patients whose precise needs they do not always understand, and the work of the general practitioner will become impossible.—I am, etc.,

Southampton General Hospital. T. N. RUDD.

Neuropathy after Thalidomide ("Distaval")

SIR,—A male aged about 40 has been under observation for some time for (?) thyrotoxicosis and/or anxiety state, and exhaustive investigations have all been negative for thyroid overactivity. A hypnotic was prescribed to assist sleep.

Early this month he complained of "fumbling" the papers on his desk and said that his hands and feet felt peculiar and that he had noticed numbness of the three middle toes of his feet. He was not addicted to alcohol and the urine was normal. Examination revealed brisk reflexes, flexor plantar responses, and absent ankle-jerks. His condition puzzled me and I had already suggested a neurologist's opinion when he asked for a repeat of his "distaval" (thalidomide). I recalled the article written by Drs. Pamela M. Fullerton and Michael Kremer (September 30, p. 855) entitled "Neuropathy After Intake of Thalidomide ('Distaval')." The patient had taken thalidomide since August, 1960, and, apart from a few brief intervals, he had taken an average of 250 mg. per night until October, 1961. It was during this month that he had noticed glove and "sock" paraesthesia. A few months earlier his finger-nails were brittle for a while, but he had not noticed any redness of the palms. He was advised to stop taking thalidomide and to report progress during the next few months.—I am, etc.,

Dorridge, Warwickshire. G. A. POWELL-TUCK.

Orthopaedics in the Tropics

SIR,—We were interested in Dr. A. J. M. Cathro's comments (August 5, p. 383) on Mr. D. R. Richard's observation (May 13, p. 1382) that good results were obtained by the conservative treatment of spinal tuberculosis in Northern Nigeria.

We do not deny that radical surgery as advocated by Roaf *et al.*[1] has given good results; but that does not mean that it is indicated. In Ibadan for the past seven years all patients without severe cord involvement have been treated as fully ambulant out-patients on isoniazid and para-amino-salicylic acid only. It is only by comparing the good results of radical surgery with the equally good results of non-surgical treatment that a conclusion could be arrived at whether radical surgery is indicated. We have found that the risk of paraplegia on the ambulant regime is more theoretical than real. Out of 207 patients reviewed, of whom 151 had no spinal cord involvement, only one patient developed paraplegia and that happened in the early weeks of treatment.

Seddon *et al.*[2] found costo-transversectomy an inadequate operation, but stated that part of their work was done before the introduction of the anti-tuberculous drugs. We now find it adequate in the paraplegias associated with paravertebral abscesses. We have reached the conclusion that the "greatest single advance in the surgical treatment of this disease" is the fact that, to a considerable extent, it has become medical.—We are, etc.,

A. BLESOVSKY.
P. KONSTAM.
S. KONSTAM.

University College Hospital, Ibadan, Nigeria.

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[1] Roaf, K., Kirkcaldy-Willis, W. H., and Cathro, A. J. M., *Surgical Treatment of Bone and Joint Tuberculosis*, 1959. Livingstone, Edinburgh.

[2] Seddon, H. J., Griffiths, D. Ll., and Roaf, R., *Pott's Paraplegia*, 1956. Oxford University Press, London.

Babies Prone or Supine?

Sir,—Dr. Nora E. R. Archer says (October 7, p. 963) it is natural for the human mother to place her infant in the supine position "unless given reasons for doing otherwise." But are not the reasons for position-preference largely cultural? In the United States, for example, almost all infants are placed in the prone position for long periods from birth. In your leading article of May 6 (p. 1304) you suggest that this practice is relatively new in America. Our experience in New York, however, is that this has been the preferred practice for at least 20 years.

In your article several arguments were advanced in favour of the prone position. Dr. Archer stresses only one: it enables the child to achieve earlier head-control. It has two other important consequences. Firstly, shifts in body-position can be more readily achieved when the infant is prone, and this is valuable in reducing restlessness. Secondly, contrary to Dr. Archer's contention, the infant can usually see more of his surroundings when prone. The supine infant can stare only at distant and rather uninteresting objects, such as the ceiling of a room. The prone infant, partly because he gains head-control relatively rapidly, surveys the objects around him.

Dr. Archer draws a distinction between sensory and motor development. Although motor development may be over-valued, it is inextricably linked to sensory development. The child who does not learn to look, feel, move, and constantly explore his environment will hardly be developing intellectually.—I am, etc.,

Marion Blank,
Visiting Child Psychologist,
Albert Einstein Medical School, New York.
Department of Medicine,
University of Cambridge.

Losing Weight

Sir,—May I please refer to your leading article entitled "Losing Weight" (September 23, p. 814), and may I please raise two points on this subject?

The first concerns diet sheets. These are often of great complexity and sometimes even surprisingly vague. (How thick is a thin slice of bread, and how big is a small piece of sponge cake?) However, their complexity is usually what bothers the patient most. Not very accurately but very conveniently the items of our diet which make fat have the initial letter "F." These are Flour, Fries, and Fat itself. Written out for the patient like this with instruction to reduce the intake of all foods containing these items will greatly simplify dieting.

The other point concerns anorectics. The obese patient is greedy for support of his willpower and hungry for help with his psychological make-up. Temporary, slight (and possibly dangerous) though the use of anorectics may be, it is cruel not to prescribe them in the treatment of obesity.—I am, etc.,

Irlam, Lancs. M. Priest.

Fainting and Dental Anaesthesia

Sir,—During the past 25 years I have administered gas anaesthesia for dental extractions for about 700 patients. In this period I can recall about six cases in which signs of collapse appeared during the administration, and I now believe that the patients had fainted under the anaesthetic, which Bourne[1] has shown can happen. In each case there was delayed recovery of consciousness.

In one instance the patient, aged about 35 years, suddenly stopped breathing and became cyanosed. After respiration had returned, he became maniacal and completely uncontrollable, this being similar to Case 5 described by Bourne. On another occasion, a man of 65 collapsed under anaesthesia, and after recovery of consciousness, which was delayed, he remained in a stuporous condition for at least 30 minutes. He stated later that for the following week he felt extremely unwell and was unable to think clearly. In each instance gas was administered in the upright position, and when respiration ceased oxygen was administered, the patient remaining in the upright position.—I am, etc.,

Shaftesbury, Dorset. W. M. Chapman.

References

[1] Bourne, J. G., *Lancet*, 1957, 2, 499.

The Tiger's Nose

Sir,—I have only recently found time to read the account of Sir Victor Negus's lecture on the protection of the respiratory tract (September 16, p. 723).

This is indeed a learned and fascinating exposition, but it contains one inaccuracy to which I should like to draw attention. In Text Fig. 3 there is a representation of the upper respiratory passages of the tiger, and it is stated that a keen sense of smell is of great value to this and other carnivora when tracking prey. Hunters and other students of big game[1 2] are, however, unanimous that tigers and other large carnivora of the cat tribe find and stalk their prey solely by eye and ear, and if they have any sense of smell at all they seem to ignore it. It is certainly not necessary to keep down wind when approaching a tiger as it is, for instance, when stalking a deer.

This shows how easily a teleological explanation can lead to a mistaken conclusion.—I am, etc.,

Esbank, Midlothian. W. T. Simpson.

References

[1] Corbett, J., *Man-eaters of Kumaon*, 1952. Oxford University Press, London.
[2] —— *Jungle Lore*, 1953. Oxford University Press, London.

Shorvon Memorial Research Fund

Sir,—Our friend Joe Shorvon, who died so prematurely in May last, at the early age of 54 and at the height of his powers, will be remembered by very many of his colleagues in general practice. He was one of the few for whom the practice of his calling was a passion, and he gave nearly all of his waking hours to the treatment of patients suffering from psychiatric illnesses. As a therapist he was unusually gifted, matching intelligence with intuitive sensibilities, flexibility in the choice of treatments with a persistent determination to give all the aid possible. Warm-hearted, generous, and modest, he made himself loved by his patients and his colleagues. His family and friends are anxious that his name should not be forgotten and that his devoted work should have an adequate memorial.

Our aim is to open a memorial fund, in the belief that not only his colleagues but also his old patients, for whom he did so much, will want to contribute to it. It is

hoped to raise a substantial sum which will be given to the Institute of Neurology for the support of research into psychiatric disorders. If, as we hope, this appeal meets with the success it merits, it could bring the day nearer when there would be an academic department of psychiatry at the National Hospital with the resources to play a worthy part in the advancement of medicine. The fund will be called "The Shorvon Memorial Research Fund." Gifts to the Fund should be addressed to the Secretary, The National Hospital, Queen Square, London W.C.1, and endorsed "Shorvon Memorial Fund."

In bringing the appeal to the notice of your readers, we hope that they in turn will acquaint those of their patients who were helped by Joe Shorvon of this opportunity to express their gratitude to him and their faith in his art.—We are, etc.,

MACDONALD CRITCHLEY,
Chairman of the Medical Committee.
MICHAEL KREMER,
Dean of the Institute of Neurology.
ELIOT SLATER,
Physician in Psychological Medicine.

The National Hospital,
London W.C.1.

Shortage of Nurses

SIR,—Miss Lilian M. Darnell's letter (September 9, p. 713) does not offer some of the "good reasons" for which I was hoping (August 5, p. 384). I am well aware that there must be selection to ensure that only those reasonably capable of successfully completing the course for State registration are given vacancies for it; and that there have been some bitter disappointments in the past. I would therefore be only too happy to see such selection made by the hospital authorities in the United Kingdom, but, as I pointed out in my previous letter, this selection is left by many hospitals to the Ghanaian Government.

Furthermore, the Ghanaian nurses to whom I referred are already qualified on the national nursing register, as I made clear; and, although the standard may be somewhat lower than that of S.R.N., it is not so much lower that they can be excluded from the category: reasonably capable of successfully completing the S.R.N. course. They are therefore unlikely to suffer any bitter disappointments as might happen if they were raw recruits to the nursing profession.

While accepting the argument that they would help the nursing shortage only while student nurses, temporary relief of the problem is better than no relief. Besides, how does such a situation differ materially from that in which a large proportion of British S.R.N. trainees are lost in marriage soon after (and in many cases even before) qualifying? This help is similarly only temporary, and the remedy would be the same for both groups—that is, they would be replaced by new recruits. Finally, there is *no* lack of suitable employment at home for S.R.N.-qualified Ghanaians.—I am, etc.,

Kwahu Hospital,
Mpraeso, Ghana.

D. H. BARHAM.

SIR,—A first-year nurse of 18 had to "lay out" 12 bodies in one week. Does this "undertaking" really help recruiting in Great Britain?—I am, etc.,

London W.2.

A. FRANKLIN.

Shush!

SIR,—Dr. Augusta J. Bonnard (September 30, p. 899) cites a method of quietening a howling baby. Instead of the automatic "shush" she uses deliberate speech behaviour and quietude. Urgently called, she finds the crying baby joggled on the arms of a relative of a terrified, horror-stricken family group. She takes the child, wrapping it firmly in blankets and shawl, inverts the child into a darkened pram, and the "miracle" results. The baby passes into a frightening trance-like state resembling death. She attributes this to a mixture of surprise, recovery of self-awareness, and exhaustion of the infant.

Her dynamic actions silence the relatives, cutting out mechanical, auditory, and light stimuli, change the mother figure, completely immobilize and invert the screeching infant. She performed what is erroneously described as "animal hypnosis," related to the active paternal induction with passes and pressure associated with Mesmer and the stage. The resultant sudden silence would not have frightened Freud. For in between his distinguished neurological and psycho-analytical careers he was an interested observer and practitioner of hypnotherapy. It is therefore most delightful to read of a Freudian (analyst) unconsciously recommending the return to the use of hypnosis.—I am, etc.,

Sidcup, Kent.

LOUIS A. NICHOLS.

POINTS FROM LETTERS

Nuclear War

Dr. JANE H. THOMPSON (Morpeth) writes: The thought expressed by Dr. P. Marioni (October 14, p. 1026) must be exercising the minds of many thoughtful people. . . . No doubt there are medical associations in Russia and her satellites, and perhaps even in China, with whom we could make contact, and what of the World Health Organization? I certainly support Dr. Marioni and await to help in any scheme which our British Medical Association may decide could be useful. The world is very sick and needs to be healed.

Dr. MALCOLM SEGALL (Hammersmith Hospital, London W.12) writes: Medical people are concerned with the preservation of life and health in a way that no other group of workers can boast. On the subject of nuclear weapons, however, there appears to be a paucity of interest in the profession. The struggle against these agents of death and disease seems to be the prerogative of philosophers, churchmen, and theatrical people. Yet for us to go about the everyday practice of medicine and ignore a threat to humanity which, if consummated, would negate all our efforts seems paradoxical and ludicrous.

Dr. ALUN J. WALTERS (Exeter, Devon) writes: All members of our humanitarian profession, if we believe in the relief of suffering and the prevention of disease, should be in full agreement with the letter of Drs. A. A. Clark, J. W. Cook, and others (October 7, p. 964). May I suggest that all members of the medical profession who refuse to use nuclear devices in the defence of principles, whether religious or political, should protest in the form of a petition to the British Government, the reason being that we will not contemplate the total destruction of humanity in order to defend principles.

What the Doctor Said

Dr. JEAN M. MOORE (Nailsworth, Glos.) writes: I can add to Dr. F. R. C. Casson's "What the Doctor Said" (September 30, p. 900) with the following item. At an infant welfare clinic I had told a mother to give the baby plenty of liquids. She was later heard telling a friend, "The doctor said I've got to give him plenty of liquorice ('licrish')."

Obituary

S. J. SCOTT, M.B., Ch.B., F.R.C.S.Ed.

Dr. Stanley J. Scott, who died suddenly while on holiday in Jersey on September 25, was a well-known general practitioner in Prestwick, Ayrshire. He was 55 years of age.

Dr. Hugh Paterson writes: Stanley James Scott was born on May 25, 1906, in Alexandria, Dunbartonshire, and was educated at Dumbarton Academy and Glasgow University, having a brilliant scholastic career at both. He graduated M.B., Ch.B. in 1929, and, after hospital appointments in places as far apart as Rochdale and Falkirk, he became a Fellow of the Royal College of Surgeons of Edinburgh in 1933. He settled in general practice in Prestwick, and there his surgical abilities were soon recognized, and he very quickly became the senior orthopaedic surgeon in Ayr County Hospital and Seafield Children's Hospital, appointments which he held until 1948. With the advent of the National Health Service he decided to devote himself to his already extensive general practice. With his partners (Drs. MacKechnie, Murray, and Boyd) he built this into one of the biggest and best-run practices in the West of Scotland. Long before official sources even thought of the long waiting-time spent by patients attending their own family doctor, Stanley Scott had instituted in his own practice a very efficient appointments system. This was an example of the meticulous attention to detail which characterized him, not only in his work but also in his hobbies and sports. He was a past chairman of the Ayrshire Division of the B.M.A. and remained a keen supporter till his death. A very keen golfer, he was a member of Prestwick Golf Club, achieving a high degree of proficiency at the game, again by unremitting attention to detail. Of recent years Dr. Scott became very interested in painting and photography, and became an enthusiastic member of Ayr Sketch Club. To his friends' eyes, at least, many of his later efforts in water-colours had about them a touch of almost professional excellence.

Our sympathies go to his wife, two daughters, and son, whom we all hope will soon fill his father's place in the B.M.A.

Mr. A. B. Kerr writes: To those of us who knew Stanley Scott in his student days it was even then clear that he was destined to stand out among his fellows. Alongside the ability which earned him many academic distinctions there was already apparent the sincerity and humanity which were to mark his subsequent career. As a local practitioner he gave himself liberally to surgery in the Ayr hospitals, but, under the National Health Service, there was no opportunity to combine surgery and general practice there. The choice having been made, he continued to attract an increasing practice, the bounds of which extended far beyond the Ayrshire coast. Patients returned to him from far and near under the spell of his manifest ability and integrity.

He was greatly blessed in his family life. The "Peter Pan" qualities of the parents almost eliminated the distinction between parents and family. It may be argued that violent sports are not for grandfathers: it would have pleased Stanley Scott that, minutes before his death, he should have been water ski-ing with his son.

SINCLAIR MILLER, D.S.O., *M.C.*, M.D., B.Sc. M.R.C.P., D.P.H.

Dr. Sinclair Miller, consulting clinical pathologist to the Royal Bath and General Hospitals, Harrogate, died on August 24 aged 76.

Sinclair Miller was born March 19, 1885. He came from a family which settled in County Derry during the "plantation" of Northern Ireland in the seventeenth century. Educated at the Rainey Endowed School, Magherafelt, he went on with a scholarship to Queen's University, Belfast, where he had a long and successful academic and athletic career. Having studied mathematics, he graduated M.A., with honours, in 1910 and B.Sc., with first-class honours, in 1912. By this time he had decided to qualify as a doctor, and the latter part of his university career he largely financed himself by winning prizes and scholarships, including the Dunville research studentship. Graduating M.B., B.Ch., again with first-class honours, in 1914, he joined the R.A.M.C. and served with distinction in France, where he found himself in command of a field ambulance almost within days of the outbreak of the first world war. He became a lieutenant-colonel, was mentioned in dispatches, and won the D.S.O. with bar and the M.C. His last military appointment was as officer in charge of the malarial research department of the 4th London General Hospital under Sir Ronald Ross. After his Army service he went to the London Hospital for postgraduate study and took the D.P.H. in 1919, proceeded M.D. (with commendation) in 1922, and took the M.R.C.P. in 1923.

T. V. P. writes: Sinclair Miller was invited to Harrogate in 1923 and for the rest of his very busy life he used that town as a centre for his pathological work in the West Riding of Yorkshire. He was on the honorary staffs of the hospitals of Harrogate, Ripon, and Keighley. Inevitably his great interest became the investigation and relief of rheumatism, but he was also an authority on the treatment of diabetes, and, what was particularly valuable in the district, he himself organized a blood-transfusion service so efficiently that in the early 1930's at any rate it was easier to arrange for blood transfusion in Harrogate than it was in London. In 1924 he founded Duchy House Nursing Home, which eventually became the only private nursing-home in Harrogate until it was purchased by the Nuffield Nursing Home Trust. He was chairman of the Harrogate Division of the B.M.A. from 1936 to 1939.

Such are the bare bones of a very active and vigorous man. Often enough he had his point of view which did not commend itself to all his colleagues, and sometimes indeed he was downright naughty. But if ever a colleague was in real difficulties, Miller, for great and small, would always do the best with the utmost kindliness, however much energy and time had to be consumed. There must be many patients and doctors who are very grateful to him. He died suddenly, but not altogether unexpectedly, after a long and disabling intercurrent illness which he bore with admirable bravery.

By his first marriage he had four children, three of whom joined the profession. One of his sons is a consultant physician in Bedford.

S. S. NICHOLSON, M.B., Ch.B.

Dr. S. S. Nicholson, who had practised in Worthing for many years, died on September 4, aged 69.

Stanley Sewell Nicholson was born on January 15, 1892, and studied medicine at the University of Edinburgh, which he represented at lawn tennis. Graduating M.B., Ch.B. in 1921, he held hospital posts in Edinburgh until joining a partnership in Worthing in the following year. In addition to the work of his practice he was an honorary physician and honorary out-patient medical officer at Worthing Hospital. Popular with his patients, he was also well known in Worthing as a skilled player of lawn tennis, golf, and bridge. Owing to ill-health he had to give up his practice about six months ago.

He leaves a widow, to whom we extend our sympathy.

G. T. NEWTON, M.B., Ch.B.

Dr. G. T. Newton, who had practised in Halesowen, Worcestershire, since 1947, died on September 12 aged 44.

George Terence Newton was born in Walsall on May 11, 1917, and lived as a boy in Wednesbury. His early schooldays were at Wolverhampton Grammar School; later

he went on to the Grammar School at Dudley, where he became head boy and where his father was chemistry master. He studied medicine at Birmingham, graduating M.B., Ch.B. in 1941. After house appointments at Walsall General Hospital he entered general practice locally at Shelfield. From 1942 to 1945 he served in the R.A.M.C. In 1947 he joined the late Dr. Bland in Halesowen and spent the last 14 years of his life there.

E. I. G. writes: Terry Newton was a man of unbounded energy and enthusiasm, determined to succeed to the utmost in anything he set his mind to. He was always a keen sportsman, excelling at school and university particularly in boxing and athletics (he was a first-class sprinter and hurdler). He continued to play regularly in club hockey and cricket until his illness forced him to give it up. A member of the medical team in the annual "Doctors *v.* Clergy" fixture at Edgbaston, he was a keen supporter of the Warwickshire County Cricket Club and a past-captain and president of the Halesowen Cricket Club.

By strict self-discipline, by punctuality, and by quick perception he was able to work efficiently through a busy day in a large practice. Even so, he entered vigorously into social life. He was an excellent speaker and loved a party. Among his many interests was the St. John Ambulance Brigade, of which he was divisional surgeon. He was a past-president of the Halesowen Rotary Club. For the last six years he had been chairman of the Dudley Division of the British Medical Association. Occupied to the full in this way, it was as though Terry knew intuitively that his life was to be a short one and that he must make the most of it. Typical of the man was his courageous determination not to give in to the increasing painful incapacity which the last three and a half years of his life brought upon him. A measure of his popularity was the fact that at his memorial service the Halesowen Parish Church was filled to capacity by over 1,000 people—a remarkable tribute to the life and work of one so young.

He married Catherine Peden Smith, of Bicton Heath, Salop, in 1942. She and his three sons survive him. Their first-born son died in childhood from poliomyelitis.

P. CORRIDAN, M.D., M.R.C.P.

Dr. Patrick Corridan, honorary physician to the Hospital of St. John and St. Elizabeth, St. John's Wood, died suddenly at his home in London on September 18. He was 51.

Mr. Desmond Mulvany writes: It was with the greatest sorrow that we learned of the sudden death of Dr. Patrick Corridan. His death came as a great shock to all who knew him, and his passing will leave a gap that will indeed be very difficult to fill. Patrick Corridan, who was born in Co. Kerry, graduated M.B., B.Ch. from University College, Dublin, in 1940. After having held the post of house-physician in St. Vincent's Hospital, Dublin, he came to England during the war and was appointed medical registrar at St. John and St. Elizabeth Hospital. Later he obtained the post of medical registrar at Charing Cross Hospital. Soon after coming to London he obtained the M.R.C.P. and proceeded M.D. of the National University of Ireland. Medical circles in London were highly impressed with his ability, and when a vacancy occurred at the Hospital of St. John and St. Elizabeth he was duly elected as honorary consultant physician. Dr. Corridan was also elected consultant physician to St. Anthony's Hospital, Cheam.

Dr. Corridan proved himself to be a skilled physician in every branch of medicine. He rapidly built up a very large practice, and his unfailing devotion to his patients must have in no small way contributed to his early death. Dr. Corridan will be greatly missed not only by his ordinary patients but also by numerous clergy and nuns, to whom he was unfailingly kind. He spent many years looking after the health of Cardinal Griffin, and latterly he was the private physician to His Eminence Cardinal Godfrey. Dr. Corridan leaves a widow and two young boys, to whom we extend our heartfelt sympathies.

A. V. STOCKS, M.B., Ch.B., D.P.H.

Dr. A. V. Stocks, formerly a divisional medical officer under the Lancashire County Council and medical officer of health of Eccles and Urmston, died on September 25 after a relatively short illness. He was 73 years of age.

Arthur Vernon Stocks was born in Eccles on July 6, 1888. From Manchester Grammar School he won an open scholarship to St. John's College, Cambridge, where he took first-class honours in the Natural Sciences Tripos. After completing his medical studies at Manchester he graduated M.B., Ch.B. at the Victoria University in 1913 and B.Ch. at Cambridge in the following year. He held the posts of house-surgeon and house-physician at Manchester Royal Infirmary and then served in the R.A.M.C. during the first world war, being mentioned in dispatches for his work on the Somme. After the war he took the Diploma in Public Health in 1920 and served with the Cheshire County Council as one of their school medical officers until 1929, when he was appointed to the medical staff of the Lancashire County Council. During the period 1929 to 1948 Dr. Stocks served as medical officer of health for Urmston and was also a divisional school medical officer for Worsley and Irlam. In 1948 he was appointed the first divisional medical officer for Middleton, Chadderton, Compton, Failsworth, and Royton areas and two years later was transferred to the Eccles, Swinton, Worsley, and Irlam areas.

Dr. Stocks was held in high esteem by all who came in contact with him, and especially by the staff of the Lancashire County Council, both medical and lay, who worked with him over the years. He was president of the North-western Branch of the Society of Medical Officers of Health for the 1954–5 session and also acted as honorary secretary for one year.

He had many interests outside his immediate work and was a well-known Methodist lay preacher in the Altrincham area and had held office as Society Steward and Circuit Steward in the Methodist Church. He had also been Sunday-school superintendent at his own church for more than 20 years and had always taken an active interest in the Hartley Victoria College Committee. In addition Dr. Stocks founded the first Hale Scout Troop in 1911 and had been district commissioner for the Altrincham area and county commissioner for East Cheshire. More recently he had been assistant county commissioner for handicapped scouts, and as recently as last April his interests in the Scout movement had been acknowledged by the conferment on him of the highest award, that of the Silver Acorn.

Deep sympathy is felt for his widow and three sons.

J. P. McGOWAN, M.D., M.R.C.P.Ed., D.T.M.&H.

Dr. J. P. McGowan, who was formerly on the staff of the Rowett Research Institute, Aberdeen, died in hospital on September 22.

We are indebted to Lord Boyd-Orr for the following appreciation: John Pool McGowan had a distinguished career as a student at Edinburgh University. Having taken the degree of M.A. in 1900, he graduated M.B., Ch.B. (with first-class honours) in 1904, obtained the D.T.M.&H. (with distinction) in 1906 and the degree of B.Sc. (public health) in 1907, and proceeded M.D. (with gold medal) in 1908. He won the Vans Dunlop scholarship in materia medica and the Charles Murchison memorial scholarship in clinical medicine, and in 1907 he held the Ernest Hart scholarship of the B.M.A. He was for a time assistant to the professor of materia medica and medical jurisprudence in the University of Edinburgh, and later he worked as a

bacteriologist in the laboratories of the Royal College of Physicians of Edinburgh, to the membership of which he was elected in 1913.

In the first world war he served as pathologist in a hospital in France, and in 1922, after a further period of research in the Edinburgh medical school, he joined the staff of the Rowett Institute. There he carried out fundamental research, applying the results to the elucidation of the causes of disease in farm animals and writing many papers on the subject. His chief publications were books entitled *Pernicious Anaemia, Leucaemia, and Aplastic Anaemia* (1926) and *On Rous, Leucotic and Allied Tumours in the Fowl* (1928).

Among his fine qualities was his love of nature. The children of the writer of this appreciation remember with pleasure Saturday afternoon rambles in the country with Dr. McGowan and his family. Two of his three children graduated in medicine: a son, William, went to a public health post in Southern Rhodesia, and a daughter, Rowla, married a senior official of the East of Scotland College of Agriculture.

MONICA LOW, M.R.C.S., L.R.C.P.

Miss Monica Low, ophthalmic surgeon to Lytham Hospital, Lytham St. Annes, died on September 26 at the age of 57.

D. R. writes: By the death of Monica Low in the prime of her life, Lancashire has lost a well-known and greatly respected figure. Born on April 13, 1904, she was the youngest daughter of the Rev. A. E. Low, vicar of St. John's Church, Folkestone, and later of St. Luke's Church, Matfield. Educated at the Cheltenham Ladies' College, she studied medicine at the London School of Medicine for Women (the Royal Free Hospital), and after qualifying in 1933 she took up ophthalmology as her career. She held junior posts at Accrington, the Manchester Eye Hospital, and the old Eye and Ear Infirmary at Myrtle Street, Liverpool.

While she was registrar at Wolverhampton and Midland Counties Eye Infirmary there grew up a friendship with Miss Hipkins, who was then matron of the Infirmary. Miss Hipkins retired from that post to become her secretary and friend, and from that time they were seldom seen apart and Miss Hipkins remained with her throughout her final illness.

Monica Low bought a practice in Blackpool, where she lived for the greater part of her professional life, and was ophthalmic surgeon to the War Memorial Hospital and the Lytham Hospital. She was also on the staff of the ophthalmic unit at Southport General Infirmary from 1944 to 1957. In 1957 she resigned from Southport General Infirmary to join the staff of the Eye Department of Preston Royal Infirmary, which was much nearer to her home. Her last illness had by this time made itself manifest, and she was struggling on with the utmost fortitude through the long and painful condition which led to her death. She was a Roman Catholic, and her faith was quite astounding in the midst of such adversity.

She was very keen on her work as an ophthalmologist and well known for her kindness to her patients and her gentleness to all those with whom she came in contact. A member of the Business and Professional Women's Club, she was a most ardent supporter of Blackpool Football Club, rarely missing a home match. Patients and friends will greatly miss her. She is survived by three brothers and one sister.

B. R. BRAMWELL, M.D., M.R.C.P.

Dr. B. R. Bramwell, who moved to Reading from Norwich some years ago, died suddenly in hospital on September 28. He was 57.

Bernard Roy Bramwell came to Norwich in 1938 after a brilliant early career at Manchester. He graduated M.B., Ch.B. at Manchester University in 1930, proceeded M.D. in 1935, and obtained the M.R.C.P. in 1937. During this period he held the posts of medical registrar and chief medical assistant in the Department of Clinical Investigations and Research at Manchester Royal Infirmary. After coming to Norwich as partner to the late Dr. Frederick Preston, he quickly built up an extensive general practice. During the war, himself being unfit for service with the armed Forces, Bramwell accepted the post of temporary honorary physician to the Norfolk and Norwich Hospital. Here in those days of staff shortages, until the end of the emergency, he rendered invaluable service, for which those connected with the hospital must always be grateful.

Modest and retiring, he devoted himself to his work. Probably few of his colleagues knew him really intimately, but he accepted the chairmanship of the Norwich Division of the B.M.A. in 1947–8. Conscientious to a degree, he was a lone worker, disdaining the services of a secretary even though this involved working until the early-morning hours. Among his many patients Bramwell's sudden decision in 1953 to forsake Norfolk for the south of England caused great sadness. By those of us who worked with him he will be remembered as a loyal and generous colleague; by his patients as a true friend and trusted doctor.—B. M.

LAMBERT C. ROGERS, C.B.E., M.D., M.Ch., M.Sc. F.R.C.S., F.R.C.S.Ed., F.R.A.C.S., F.A.C.S.

The obituary of Professor Lambert Rogers was published in the *Journal* of October 21 (p. 1089).

J. C. N. writes: I should like to add the appreciation of an old friend to what has been said in tribute to Professor Lambert Rogers. We first met during the early part of the last war and became close friends during a voyage from Australia which formed the latter part of his honeymoon in 1952. No doubt others with greater experience of his professional achievements will speak with more authority on the subject than I can. He was indeed a most modest man, but there is little doubt that as a teacher and administrator he exercised great influence which extended far beyond the confines of the university in which he occupied the chair of surgery for 26 years. His special interest in the surgical aspects of diseases of the spinal cord also produced results of exceptional value. It is, however, mainly on account of the quality of his personal character that his many friends will remember him with the greatest affection. His friendliness and charm and the unbounded kindliness with which he treated everyone with whom he came in contact made him a most popular man among his fellows; while these same qualities, combined with an abiding love of travel and of ships and the sea, made him friends among surgeons all over the world, so that he became a sort of surgical ambassador in the tradition of his old friends Sir Gordon Gordon-Taylor and Professor Grey Turner.

As mentioned elsewhere, one of the most outstanding features of his character was his highly developed sense of loyalty. This particularly extended to his old chiefs and colleagues but also included his more recent friends and juniors and many institutions he served so faithfully; it even extended to his old car. The last letter he published in this journal, earlier this month, concerning intramuscular injection, was completely typical in quoting the authority of his much admired old chief and friend, Grey Turner, rather than submitting the opinion expressed as his own. Those of us who were privileged to hear him deliver his memorial lecture to Grey Turner in Dublin last month will no doubt recollect this same characteristic. Incidentally this lecture entailed considerable personal effort in his precarious state of health and, alas, was to be his own swan-song. In it he said practically nothing about himself but much about the life and work of Grey Turner and also about the great surgical contemporaries he admired so much, among them Sir John Bland-Sutton, under whom he had served as dresser at the Middlesex; Webb-Johnson, whose house-surgeon he was;

Grey Turner, whose first assistant he had been at Hammersmith; and, lastly, probably his greatest friend and surgical hero among his seniors, Sir Gordon Gordon-Taylor.

Although his great knowledge of surgery combined with an original quality of mind made his opinions always worth hearing, yet he loved to quote the great masters of his craft in preference to stating views of his own.

No account of Lambert's life would be complete without reference to the guiding influence of his deep but simple religious faith; though tolerant of the failings of others he had the highest standards for his own conduct in all things. His last few years were clouded by an obscure malady about whose outcome he had no illusions. He fully realized that he "walked through the valley of the shadow of death" but like the Psalmist and for similar reasons he "feared no evil." He carried on as far as he was physically able up to the end. Although his many friends will deeply miss him and deplore his loss while still at the height of his intellectual powers, yet his life's work was virtually finished, and at least he was spared the prolongation of chronic illness and inevitable decline.

In a recent conversation with me concerning a mutual friend, Lambert summarized his opinion by simply stating, "He is a Christian gentleman." I can think of no more fitting description of Lambert Rogers himself.

Medico-Legal

OPERATING ON THE WRONG PATIENT OR WRONG PART OF A PATIENT

We print below a joint memorandum of the Medical Defence Union and the Royal College of Nursing on the steps that might be taken to obviate the risk of a surgeon performing an operation on the wrong patient, side, limb, or digit.

MEMORANDUM

The Medical Defence Union and the Royal College of Nursing have given consideration to the steps that might be taken to obviate the risk of an operation being performed on:

(*a*) the wrong patient,

(*b*) the wrong side,

(*c*) the wrong digit.

During the period October, 1959, to September, 1961, the Medical Defence Union dealt with no fewer than twenty-eight such cases and it is hardly necessary to say that these avoidable mistakes are quite indefensible.

The Councils of the Medical Defence Union and the Royal College of Nursing are firmly of the opinion that in order to minimise the risk of such occurrences, it is eminently desirable that wherever practicable the suggested safeguards as outlined below should be taken. It is appreciated that in certain out-lying or "cottage" hospitals there is no resident medical staff and that in some hospitals it may not always be possible to adopt these safeguards in their entirety.

(*a*) OPERATING ON THE WRONG PATIENT

Causes Predisposing to Error

(i) In hospitals which undertake a vast amount of casualty work where emergency patients are being admitted in quick succession, some of them unconscious, there is the possibility of the notes becoming attached to the wrong patient. Where it is the practice to attach the patient's name to the clothing which has been removed in the casualty department, this does not always provide an adequate check because the clothes may be detached from the patient before or on admission to the ward.

(ii) In respect of patients for non-emergency operations who have been in the ward for a day or two prior to operation, mistakes may arise if on the day of operation the beds are changed round. This situation is exacerbated if the day of operation coincides with a change in several of the nursing staff and could lead to the wrong patient being sent to the theatre if the routine did not provide adequate safeguards against error.

(iii) Mistakes may occur when changes are made in theatre lists following the commencement of the operating session, particularly if such changes have not been notified to the ward immediately they have been made.

Suggested Safeguards

(1) All unconscious patients admitted through the casualty department should be labelled before they are taken to the wards. The identity disc or label should bear the patient's name, initials and hospital number where possible. The labelling of the patient should be the responsibility of the casualty sister or her deputy, or by night, the nurse-in-charge or her deputy.

(2) Following the admission to hospital of a patient who is to undergo an operation, he should be seen in the ward by the surgeon who is to perform the operation. Prior to the operation the surgeon should examine the patient's records and make sure that the notes do in fact relate to that particular patient and that the entries contained therein are correct.

(3) All patients going to the operating theatre should be labelled by means of an identity disc or label attached to the wrist or ankle. The identity disc or label should bear the patient's name, initials and hospital number. The labelling should be carried out in the ward at the time the patient is prepared for the operating theatre and should be the responsibility of the ward sister or her deputy.

In rare cases where the patient goes direct from the casualty department to the operating theatre, the onus of correct labelling should rest on the casualty sister or her deputy. In either instance the labelling would constitute an additional check that the correct patient received the prescribed premedication and that the correct patient was sent to the theatre.

(4) In addition to the nature of the operation, the patient's name, initials and hospital number should also appear on the operation list. A copy of the operation list should be displayed in the anaesthetic room as well as in the operating theatre, thus enabling both the anaesthetist and the surgeon to check and ensure that the right patient is presented for operation. A copy of the operation list should also be made available to wards in which the patients who are to undergo operation are accommodated.

(5) Patients should be sent for from the operating theatre by name and number and never as "the patient from such and such a ward." Where it is the practice for a porter from the theatre to collect the patients from the ward he should bring with him a slip bearing the name of the patient and his hospital number. In hospitals where the procedure is to telephone the ward to ask that the patient concerned be sent to the theatre, the patient's hospital number, as well as the name, should be quoted. The ward sister or her deputy should be responsible for seeing that:

(*a*) the correct patient is sent to the operating theatre;

(*b*) the patient has already signed the appropriate consent to operation form;

(*c*) the patient has received the prescribed pre-operative preparation including premedication;

(*d*) where appropriate the side of operation has been marked (see Section (*b*) Clause (1));

(*e*) the correct case papers, *x*-rays, etc., accompany the patient to the theatre.

(6) In the operating theatre one person should be made responsible for sending for patients. This should be the responsibility of the theatre superintendent but in large operating theatre suites it may be necessary for her to delegate this responsibility to some other person, e.g., the sister-in-charge of a particular theatre or the nurse taking the list in a particular theatre.

(7) When out-patients are admitted to the wards for the day for a minor operation, they should be labelled in the same way as in-patients before they are taken to the operating theatre.

(8) Patients who are to be operated on in the out-patient theatre under a general anaesthetic should be labelled in the same way as the in-patients.

(9) Patients should have one hospital number which should be quoted on all papers concerning the patient. Where it is the practice to have departmental numbers these may be used additionally on the appropriate papers but never exclusively.

(10) In so far as children are concerned, the labelling should be carried out when they are admitted to the ward. As the case histories must be taken from the patient's relatives (who may not be present immediately prior to the operation) it is vital that no error should occur in these notes in reference to the side, limb or digit on which the operation is to be performed.

(*b*) OPERATING ON THE WRONG SIDE OR LIMB

Causes Predisposing to Error

(i) Wrong information on the case papers of the patient, i.e., "right" instead of "left."

(ii) Abbreviation of the words "right" and "left."

(iii) Illegible writing on the case papers.

(iv) Failure to check immediately prior to commencing to operate the entry on the operation list with the notes taken to the operating theatre.

(v) The wrong case papers accompanying the patient, combined with (iv) above.

(vi) The preparation of the wrong side or limb, combined with (iv) above.

(vii) No routine procedure for marking the operation side.

Suggested Safeguards

(1) The side on which the operation is to be performed should be indelibly marked before the patient reaches the theatre, and in order to denote the side a mark should be made with an indelible skin pencil on the forehead of the patient. This should normally be made the responsibility of the house surgeon. In the case of "listed" patients already in the ward, it is usual for the house surgeon or a house officer to see the patient on the evening before the operation and this would give the practitioner concerned an opportunity of marking the operation side. In the case of emergency operations the surgeon generally sees the patient in the ward before he is taken to the operating theatre, thus providing him with an opportunity for marking the operation side. In the rare instance of a patient who is taken direct from the casualty department to the operating theatre, the practitioner who decides upon an immediate operation should be made responsible for marking the operation side.

In the event of the ward sister or her deputy, or exceptionally the casualty sister or her deputy, finding that the side of operation has not been marked when the patient is due to be sent to the operating theatre, she should see that the surgeon who is to operate is informed accordingly, but she should not herself undertake the marking.

(2) The words "right" and "left" should be written in full in the patient's notes and in the operation list.

(*c*) OPERATING ON THE WRONG DIGIT

Causes Predisposing to Error

(i) Fingers referred to by numbers instead of by name.

(ii) Wrong information on the case papers of the patient, i.e., "right" instead of "left."

(iii) Illegible writing on the case papers.

(iv) Failure to check immediately prior to commencing to operate the entry on the operation list with the notes taken to the operating theatre.

(v) The wrong case papers accompanying the patient, combined with (iv) above.

(vi) The preparation of the wrong digit combined with (iv) above.

(vii) No routine procedure for marking the side on which the operation is to be performed.

Suggested Safeguards

(1) In order to avoid the possibility of any ambiguity concerning the finger(s) on which the operation is to be performed, the finger(s) should always be described as thumb, index, middle, ring and little fingers and not as 1st, 2nd, 3rd, 4th and 5th. In so far as the toes are concerned, the accepted practice is to describe them as hallux (big), 2nd, 3rd, 4th and 5th (little) toes and this should always be adhered to.

(2) The words "right" and "left" should be written in full in the patient's notes and on the operation list.

In order to reach agreement on a routine procedure, incorporating as far as possible the safeguards put forward in this memorandum, to be adopted in a particular hospital or group of hospitals, it is suggested that joint committees of medical and nursing staff should be set up on a local basis. The committees should include, *inter alios*, the matron and a representative of the consultant surgical staff.

Medical Notes in Parliament

TOBACCO ADVERTISING

[From our Parliamentary Correspondent]

Mr. Francis Noel-Baker, who sits as Labour M.P. for Swindon, is a persistent critic of what he regards as anti-social expenditure on advertising, and high on the list he places the tobacco firms' campaigns. He seized one of the three opportunities presented by the earlier recall of Parliament to mount another attack on October 18. This was based on recent work with the Advertising Inquiry Council, a non-political consumer organization, which has in preparation a long and documented report on tobacco advertising.

Cigarette-smoking and Health

Mr. Noel-Baker recalled the Medical Research Council's report of 1957 and the more recent surveys of smoking habits among secondary schoolboys, and asked the Government spokesman to restate the Government's general attitude to cigarette-smoking and its effect on health, and to smoking by young people. Teachers, parents, and relatives had a responsibility towards children and youngsters to do everything they could to prevent them getting into the habit of smoking cigarettes. Had not the Government a much wider responsibility for the health and lives of millions of young people who were being assailed by a £20m.-a-year campaign of commercial propaganda designed to make them start smoking and then keep on smoking? If the tobacco companies were not convinced that these enormous sums were having a substantial effect in increasing sales they would not be spending such sums. Statistics showed a substantial increase in spending on tobacco and cigarettes: for the calendar year 1960 it was £1,140m., of which £1,002m. was on cigarettes. From this the Government

derived a total revenue of £826m. Many people wondered whether their soft attitude to the tobacco industry was not influenced by the enormous revenue derived from it.

Campaigns Aimed at Young People

What Mr. Noel-Baker wanted the Government to do was this: (1) To issue a strong warning to tobacco manufacturers that unless they called off all advertising campaigns—press, poster, television—aimed directly or indirectly at young people, the Government would take action to restrain them. (2) Impose another stiff increase in taxation on cigarettes in the next Budget. The only Government measure so far that had been effective in causing a temporary drop in consumption had been the big increases in tax, particularly in 1947 and 1948. (3) A dramatic increase in the efforts of the Government and local authorities to warn schoolchildren and teenagers of the dangers of lung cancer and other diseases caused by cigarette smoking. The money spent so far on these purposes had been no more than a miserable trickle.

Sir Cyril Black, Conservative member for Wimbledon, briefly demonstrated the non-party character of the concern expressed.

Government Reply

Mr. Niall Macpherson, Parliamentary Secretary to the Board of Trade, began with the assertion that there had been no modification in the views stated by the Government in 1957 that the facts stated in the Medical Research Council's report should be brought to public notice so that everyone might know the risks involved in smoking and individually make his own choice. Small-scale surveys had since supported the view that the local authorities' publicity campaigns had been effective in bringing the matter to attention. For example, one in Edinburgh showed that 98% of the people approached knew of the possible connexion between lung cancer and smoking—though he suspected that some of those interviewed felt there was nothing in the report likely to affect them personally. There could be few, he claimed, who were not aware of the risks of heavy smoking. "The choice is theirs. The fact that some people may misuse that choice is not a good reason for damaging their freedom of choice."

No Marked Increase in Consumption

He argued—without accepting the figure of £20m.—that, colossal as had been the rise in expenditure on tobacco advertising campaigns, it had not been accompanied by any marked increase in consumption. Retail sales for the first half of the year were estimated to be 133 million lb., compared with 130 million in the first half of 1960 and 124 million in the first half of 1959. Much of the increase in advertising expenditure might well be attributable to the introduction of commercial television, but it seemed that the effect had been rather to increase competition among brands than to increase consumption generally. Broadly speaking, consumers tended to remain loyal to the brand of their choice, and much of the increase in advertising seemed to be due to new brands seeking to appeal to young people before they had become committed to any particular brand. That, he imagined, was why tobacco advertising was directed to youth. He doubted whether public opinion would support a prohibition on advertising tobacco. It had been banned in Sweden, but consumption had not fallen.

Up to Individual to Choose

What should be done? They should continue to seek to ensure that the public, and particularly parents, teachers, and those in daily contact with the young, were continually reminded of the facts and encouraged to make aware to those in their charge of the dangers of smoking. The young people, he believed, were intelligent enough to draw their own inferences. It was for the individual to make his choice, freely. It was for the Government to ensure that he made it in full knowledge of the facts.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Lord Adrian, O.M., M.D., F.R.C.P., F.R.S., Master of Trinity College, has been appointed a Deputy Vice-Chancellor of the University for the academic year 1961–2.

UNIVERSITY OF ABERDEEN

The following appointments are announced: Dr. Eric McKay, Lecturer in Child Health, from a date to be arranged: Dr. K. J. Dennis, Lecturer in Midwifery and Gynaecology, from October 1, 1961; and Dr. J. R. Greig, terminable Lectureship in Anatomy, from October 1, 1961.

Dr. N. G. Fraser resigned from the Lectureship in Mental Health on October 15, 1961.

Vital Statistics

Poliomyelitis in Hull

The mass administration of oral vaccine to combat the outbreak of poliomyelitis at Hull (see *Journal*, October 21, p. 1091) was completed on October 24, by which time about 360,000 infants, children, and adults had received the vaccine. An immunization campaign has since been undertaken in a neighbouring urban district. Up to October 24 there had been 67 cases of poliomyelitis in Hull, 21 of which were notified between October 17 and October 24.

Poliomyelitis in Sheffield

Between September 13 and October 24 there have been 14 cases (11 of them paralytic) of poliomyelitis in Sheffield. Most of the patients are children under 10 years of age. Only one had received a course of two injections of Salk vaccine (in 1958) and one other had had one injection: the rest were unprotected.

Infectious Diseases

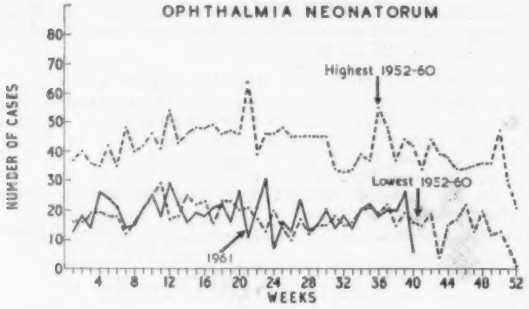
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

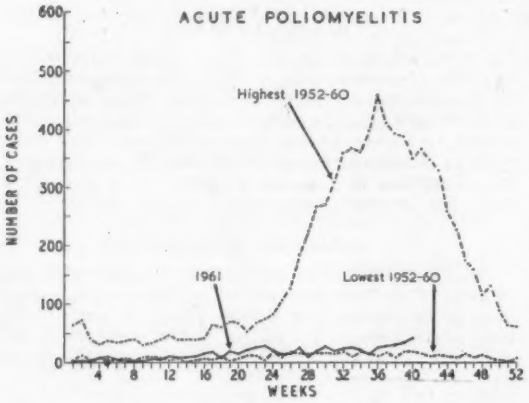
	Week Ending Oct. 7	Oct. 14
Acute Poliomyelitis		
Lancashire	12	17
Bolton C.B.	4	7
Yorkshire East Riding	9	29
Kingston-upon-Hull C.B.	9	29
Dysentery		
Cornwall	6	16
Penzance M.B.	1	12
Lancashire	77	97
Liverpool C.B.	26	28
Glasgow	108	103
Edinburgh	24	35
Dundee	23	34
Paratyphoid Fever		
Durham	1	4
Houghton le Spring U.D.	0	4
Wiltshire	0	3
Salisbury M.B	0	3
Glasgow	1	4
Food Poisoning		
Lancashire	40	48
Liverpool C.B.	10	24

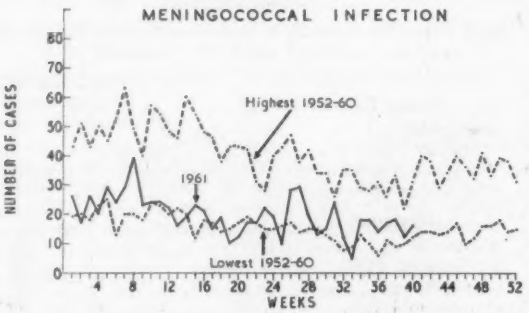
Graphs of Infectious Diseases

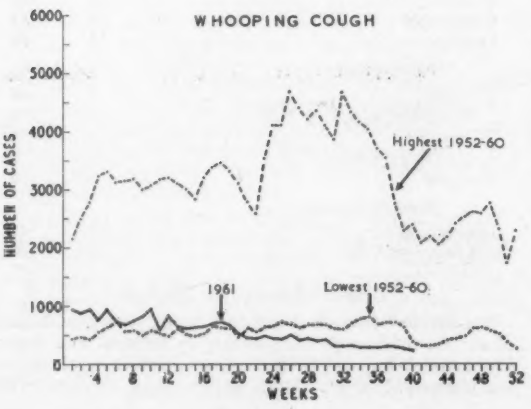
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for

1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 7** (No. 40) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	1	0	2	0	1	3	0	0	0	1
Dysentery ..	314	25	210	13		500	112	148	26	7
Encephalitis, acute	7	1		0		3	2		0	
Enteric fever:										
Typhoid ..	3	1	2	0		4	1	1	2	
Paratyphoid ..	2	0	4(B)	0		7	0	0	0	
Food-poisoning ..	243	22	22	2		225	19	26	4	
Infective enteritis or diarrhoea under 2 years				20	17				16	40
Measles*	1,052	40	15	37	32	2,853	112	71	4	9
Meningococcal infection	16	0	5	0	1	28	2	7	0	
Ophthalmia neonatorum	6	0	6	0		16	1	3	0	
Pneumonia† ..	110	8	104	0	1	199	13	113	0	1
Poliomyelitis, acute:										
Paralytic ..	35	0	1	0	1	14	4	0	1	10
Non-paralytic ..	7	0	0			4	1	1		
Puerperal fever§ ..	174	30	8	0		194	35	4	0	1
Scarlet fever ..	248	22	39	14	11	357	31	54	32	24
Tuberculosis:										
Respiratory ..	288	29	48	11		385	53	63	9	
Non-respiratory	39	6	7	3		46	8	7	3	
Whooping-cough	221	10	22	7	4	1,021	90	113	5	24

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	1	0	0	0	1
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	1	0	1	7	0		0	1
Influenza	3	0	0	0	0	7	0	1	0	0
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	399	37	13	11	6	467	38			5
Poliomyelitis, acute	4	0		0	0	0	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	60	6	3	0	1	57	4		1	1
Non-respiratory		1		0	0		0		0	0
Whooping-cough	2	0	0	0	0	0	0	0	0	0
Deaths 0–1 year ..	319	34	20	10	23	326	33	37	4	6
Deaths (excluding stillbirths) ..	8,780	734	505	120	155	9,480	755	530	116	135
LIVE BIRTHS ..	15,962	137	1057	279	406	15,833	1317	1136	301	354
STILLBIRTHS ..	281	35	20			309	32	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Nobel Prize for Medicine

This year's Nobel Prize for medicine—worth about £17,250—has been awarded to Professor Georg von Békésy, Senior Research Fellow at Harvard University, for his work on the physiology of hearing. Professor von Békésy, who was born in Budapest 62 years ago, worked in Berlin and Stockholm before joining the staff of the Psycho-acoustic Laboratory at Harvard in 1949. His distinction as a medical scientist has previously been recognized by the award of many honours, including the Leibnitz Medal of Berlin University and the Gold Medal of the American Otological Society. (See annotation at p. 1137.)

[*Planet News, Ltd.*

The Harveian Oration

The Harveian Oration, "The Consummation of William Harvey," was given by Sir Arthur Thomson before the Royal College of Physicians of London on October 18. "If the fetters of traditional belief with no basis but speculation were too strong for so acute a mind it is not surprising that many others did not escape them in succeeding generations," said Sir Arthur, and he went on to trace the "slow and faltering progress" made during the two centuries that followed the publication of *De motu cordis* until, in the nineteenth century, Harvey's consummation was reached and the full measure of his achievement assessed. ("The Consummation of William Harvey" will be published in full in a forthcoming issue of the *Journal*.)

Royal Society of Tropical Medicine and Hygiene

The presidential address at the opening meeting of the Royal Society of Tropical Medicine and Hygiene's new session on October 12 was given by Sir George McRobert on the theme of "Empire into Commonwealth." He recalled the fact that expectation of life in the Tropics had been increased and the secrets of many of the most dreaded diseases laid bare by the work of the Society's Fellows.

His own work had been largely done in India, and he described the country's gradual progress to emancipation. In medical education a dual system had been worked, in which the licensed medical practitioners who had taken a course of three years were allowed to practise in permanently subordinate positions; this system led to jealousies, and it was ended after independence. But Sir George argued that in emerging countries there was so great a need for doctors or assistants to carry out mass treatment, vaccination, and public health programmes that some form of dual system might still have a place. The medical help most needed by the emerging countries was not elaborate electronic equipment: after peace and security the greatest needs were for the development of agriculture, irrigation, and primary education, and for the means to combat the common debilitating diseases. Priority in research should go to work on nutrition and family limitation—the atomic bomb was not so dangerous as an atomic womb. International co-operation and teams for special investigations had become essential to cope with modern problems and could be provided, as indeed they had been in the work on Kyasanur Forest Disease and in the domiciliary treatment of tuberculosis in Madras. Sir George summed up by remarking that much of the money available from British sources should be spent on British-based research, and most of the remainder on health education.

Treatment of Carcinoma of the Breast

On October 19 about 200 members and senior medical students attended the first of the series of lecture-discussions being held in B.M.A. House this winter. Under the chairmanship of Sir Arthur Porritt, P.R.C.S., acting President of the B.M.A., Professors Hedley Atkins and Ralston Paterson spoke on the treatment of carcinoma of the breast. Professor Hedley Atkins, speaking frankly and informally, gave his own personal views on surgical treatment, dwelling particularly on the early case. Considering the wide spectrum of opinion on the subject, he thought the wisest thing to do was the sensible thing to do, and in his view the sensible thing to do was radical mastectomy. But it was quite justifiable that other methods should be tried with all the discipline of a controlled trial. Having discussed the indications for oophorectomy, hormone treatment, and adrenalectomy and hypophysectomy, he ended by saying that a controlled clinical trial with cortisone was in progress to see whether it could achieve the same results as adrenalectomy and hypophysectomy. Professor Ralston Paterson then gave a clear exposition, well illustrated with graphs showing the effects of treatment on cancer in various stages, of what radiotherapy had to offer in the treatment of carcinoma of the breast. In really advanced cases with metastases radiotherapy could give only palliation, but a number of cases in the intermediate category, though inoperable, could still be cured by radiotherapy, while in others useful palliation and prolongation of life could be achieved. There were varying views on the place of radiotherapy in operable cases, and Professor Ralston Paterson described the conclusions they had drawn from their wide experience at the Christie Hospital and Holt Radium Institute, Manchester. The meeting concluded after the speakers had answered questions from the audience.

The next B.M.A. lecture-discussion will be held in B.M.A. House at 5.30 p.m. (tea at 5 p.m.) on Thursday, November 23, when Sir Denis Browne will talk on the early diagnosis of orthopaedic abnormalities, with Mr. H. J. Seddon in the chair.

Oral Poliomyelitis Vaccine for Routine Immunization

Mr. Powell, Minister of Health, announced in Parliament on October 24 that the Sabin oral poliomyelitis vaccine will be made available for vaccination of the priority groups (broadly, those up to 40 years of age) as soon as arrangements have been made with local authorities and the medical profession and discussions on technical matters have been completed. The Government has accepted the recommendations of the Joint Committee on Poliomyelitis Vaccination that the Sabin vaccine may be used both safely and effectively for primary vaccination; that pending further study it should not be used to complete a course of vaccination started with Salk vaccine; and that so long as Salk vaccine is available it should also be provided for primary vaccination if doctors prefer it. The trivalent form of vaccine will be used for routine immunization, 3 doses being given at intervals of 4 to 8 weeks.

Royal College of Surgeons of Edinburgh

Professor John Bruce has been re-elected President and Professor N. M. Dott re-elected Vice-president of the College. Professor Bryan McFarland has been elected a Vice-president.

Chairman, United Leeds Hospitals

Sir Donald Kaberry will succeed Sir George Martin as chairman of the board of governors, United Leeds Hospitals, from November 11.

University of Leeds Medical Journal

The committee of this journal has decided, with great regret, that this publication should cease forthwith. The last issue appeared in May, 1961.

Pfizer Corporation to Sue Ministry

Pfizer Corporation has stated that the Minister of Health's purported exercise of Section 46 of the Patents Act, 1949, in obtaining supplies of certain patented drugs from unlicensed sources for National Health Service hospitals (see *Journal*, May 27, p. 1521) constitutes a serious attack on the normal patent rights of the companies who own the patents concerned. To test the legality of what the Minister has done, Pfizer Corporation (one of the patentees affected) has begun proceedings against the Ministry of

Health. These proceedings were begun before the Ministry's recently announced decision to award contracts to unlicensed suppliers (October 7, p. 968).

Grants, Gifts, and Bequests

Dr. R. A. LIGHT, an American surgeon and a graduate of St. Catherine's Society, Oxford, has given about £2,500 to provide closed-circuit television equipment in the Nuffield Department of Surgery at the Radcliffe Infirmary. He and his wife have already given shares worth £193,000 to the new St. Catherine's College.

People in the News

Dr. L. GUTTMANN, director of the National Spinal Injuries Centre, Stoke Mandeville Hospital, has been awarded the Werner Ruhemann Bronze Plaque for outstanding work in the field of sport medicine by the German Medical Association of Sport Medicine.

Dr. I. W. ROWLANDS, M.Sc., Ph.D., has been appointed Senior Research Fellow in Reproductive Physiology by the Zoological Society of London. He will be in charge of the Wellcome Institute of Comparative Physiology which is to be built in the Society's grounds next year.

COMING EVENTS

Institute of Dermatology.—Exhibition, Dr. E. J. MOYNAHAN, "The Biology of the Skin Surface," November 1–29, St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London W.C.2.

Feldberg Foundation Lecture.—Dr. HERBERT HENSEL (director, Physiological Institute, University of Marburg), "The Electro-physiology of Thermoreceptors," November 2, 5.30 p.m., Physiology Theatre, University College London, Gower Street, London W.C.1.

Association of School Medical and Dental Officers of Scotland.—Meeting, November 4, 10.30 a.m., Boots Pure Drug Company, Rawyards, Airdrie. Dr. J. BELL, "Occupational Health and the Child in Industry." Lunch available. Details from Dr. MAUD P. MENZIES, Rosmaris, 34 Rhannan Road, Glasgow S.4.

Glasgow University Club, London.—Annual dinner, November 9, 7 p.m., Trocadero Restaurant, London W.1. Chairman: Sir HECTOR HETHERINGTON. Graduates who are not members should write to Dr. J. F. HEGGIE, Department of Pathology, North Middlesex Hospital, London N.18.

Chelmsford Postgraduate School of Obstetrics.—Refresher courses in obstetrics for general practitioners: residential for two weeks (maximum two doctors at any one time); lectures and demonstrations (maximum 25 doctors). Inquiries to British Postgraduate Medical Federation, 18 Guilford Street, London W.C.1.

Royal Society of Arts.—G. H. CULLEN, Esq. (Manager, Ministry of Labour Government Training Centre and Industrial Rehabilitation Unit, Perivale), "Vocational Training and Industrial Rehabilitation," November 8, 2.30 p.m., R.S.A., John Adam Street, Adelphi, London W.C.2. Tickets from that address.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 30

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. R. F. Mahler: Glycogen Storage Diseases.

UNIVERSITY COLLEGE LONDON.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor J. N. Davidson, F.R.S.: Biosynthesis of Polynucleotides.

Tuesday, October 31

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor R. G. Harrison: Functional Aspects of the Vascularization of Tissues.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. W. K. Silvers (Philadelphia): Analysis and Implications of the Phenomena of Pigment Spread in Guinea-pig Skin.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5 p.m., Bengué Memorial Award Lecture by Dr. H. K. Beecher: Nonspecific Forces Surrounding Disease and the Treatment of Disease (illustrated).

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At London School of Hygiene and Tropical Medicine, Keppel Street, W.C., 5.30 p.m., Dr. F. Yates, F.R.S.: discussion meeting on Computers in Medicine.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. Arthur M. Sutherland: Functional Uterine Haemorrhage.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. F. Swann: Auto-tomography in Cerebral Pneumography.

WESTMORLAND COUNTY COUNCIL.—At County Hall, Kendal, 3 p.m., Dr. William Lees: Some Aspects of Morbidity Resulting from Pregnancy.

Wednesday, November 1

ABORTION LAW REFORM ASSOCIATION.—At Conway Hall, Red Lion Square, London W.C., 7.30 p.m., Miss Joan Vickers, M.P.: Status of Women Commission; Mr. R. S. W. Pollard, J.P.: Practical Problems of Getting the Law Amended.

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Professor A. Kekwick: Obesity.

BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY SECTION.—8.30 p.m., Dr. J. M Malins: Recent Trends in Diabetes.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. J. Prime: Pulmonary Lesions and Charges of Function in Chronic Bronchitis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., 40th clinico-pathological conference. Dr. I. Friedmann and Dr. D. A. Oxborn: (1) Adamantinoma; (2) Stapedectomy (Otosclerosis); (3) Malignant Granuloma of the Nose.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. W. N. Mascall: Gonococcal Urethritis.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor D. A. K. Black: Gastro-intestinal Functions.

WHITTINGTON HOSPITAL: ARCHWAY WING.—11.30 a.m., Dr. Deborah Doniach: Auto-immunity in Disease.

Thursday, November 2

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor J. J. Pritchard: Bone Healing.

COLLEGE OF GENERAL PRACTITIONERS: RESEARCH SECTION.—At Royal Society of Medicine, 6 p.m., joint meeting with Association of Medical Advisers in Pharmaceutical Industry. Discussion: Place of the General Practitioner in Therapeutic Research.

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, 5 p.m., Dr. W. M. Court Brown: Some Contributions of Human Cytogenetics to the Study of Disease.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Mr. W. M. Beattie, Dr. V. K. Summers, Dr. M. A. Stewart, and Mr. A. M. Abrahams: Carcinoma of the Breast.

LONDON UNIVERSITY.—At Royal Society of Medicine, 5 p.m., Semon Lecture by Mr. C. P. Wilson: Pharyngeal Diverticula—Their Cause and Treatment.

ROYAL SOCIETY.—10.30 a.m., discussion to be opened by Professor Wilson Smith, F.R.S.: Mechanisms of Virus Infection.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Professor Martin Roth: Mental Illness in Old Age and Some General Problems of Psychiatry.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5.15 p.m., Dr. Denis Williams: postgraduate demonstration in neurology.

Friday, November 3

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. D. F. N. Harrison: Sore Throat.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, (1) 11 a.m., discussion: Chorioncarcinoma. Guest speakers: Mr. A. Brews and Dr. W. W. Park. (2) 3 p.m., Mr. R. Cox: The Bowel and the Gynaecologist.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. A. L. Eyre-Brook: Difficulties in Diagnosis in Some Malignant Tumours of Bone.

●ROYAL INSTITUTION.—9 p.m., Dr. S. Brenner: Handing on of Genetic Information in Living Matter.

Saturday, November 4

ASSOCIATION OF CLINICAL BIOCHEMISTS: SOUTHERN REGION.—At Queen Mary's (Roehampton) Hospital, 2.30 p.m., symposium: Special Applications of Electrophoresis

MIDLAND THORACIC SOCIETY.—At 36 Harborne Road, Edgbaston, 3 p.m., Dr. J. Mackinnon: Diagnostic Techniques in Cardiology.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Bramwell.—On September 28, 1961, in hospital, Bernard Roy Bramwell, M.D., of Ashcroft, Albert Road, Caversham, Reading, aged 57.

Burnett.—On October 2, 1961, Ronald Andrew Burnett, M.B., Ch.B., of Glasgow, aged 46.

Ferguson.—On October 5, 1961, John David Ferguson, C.M.G., D.S.O., L.R.C.P.&S.I., Colonel R.A.M.C., retired, of Cassala Murdoch Road, Wokingham, aged 94.

Fox.—On September 28, 1961, at 1 Cardinal Avenue, St. Budeaux, Plymouth, Millicent Fox, M.B., Ch.B., aged 83.

McKernan.—On September 21, 1961, in London, Percy Edward McKernan, M.B., B.Ch., of 178a Wandsworth Road, London S.W., and 709 Duncan House, Dolphin Square, London S.W.

Mecredy.—On September 28, 1961, at Killiney, The Grove, Burnham-on-Sea, Somerset, Cedric Cowan Mecredy, M.B., B.Ch., D.P.H., late Captain I.M.S., aged 71.

Murphy.—On September 25, 1961, in hospital, Basil Newman Murphy, M.C., M.R.C.S., L.R.C.P., L.D.S., aged 81.

Richards.—On September 27, 1961, William Powell Earle Richards, M.B., Ch.B., of 1 Grange Lane, Bromham, Beds, aged 59.

Seex.—On October 5, 1961, at Stornoway, Ian Harry MacGregor Seex, M.B., Ch.B., F.R.C.S.Ed., of Sprinfield House, Inverness.

Williamson.—On September 26, 1961, at Papworth Hall, Cambridge, Robert Williamson, M.B., Ch.B., D.L.O., J.P., of Tudor House, Withersfield, Suffolk.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Physiological Problems of Space Flight

Q.—*What are the main physiological problems of space flight, and how can they be overcome?*

A.—(1) Radiation: cosmic rays.—Moderate shielding is necessary only on long voyages. (2) Van Allen radiation belts.—The inner belt can be bypassed at high geomagnetic latitudes; the outer belt may be safely penetrated at high speed but not lingered in. (3) Solar flare radiation.—Occurs in isolated outbursts of variable intensity, but every few years there comes one of such dangerous intensity that sufficient shielding is at present impracticable. Long voyages should not be made near periods of sunspot maximum. (4) Weightlessness.—Individual reactions vary, but they can be tested in aeroplanes for periods of up to 45 seconds. Weightlessness is now known to be tolerable for at least 24 hours by suitable subjects, but some subjects cannot tolerate sharp movements of the head while weightless, and the same difficulty arises if the ship is rotated to provide centrifugal force as a substitute for gravity. Food must be in paste form; solid or liquid food may go up the posterior nares into the sinuses. (5) Excretions.—An apparatus for dealing with them is now being tried out in the United States. Particulate impurities in the air must be prevented or filtered out, since they cannot fall out. (6) Accelerations during take-off and decelerations during landing.—Astronauts so far have not been submitted to more than 5 *g* or 6 *g*, which they can tolerate for several minutes if lying down, though greater accelerations would make the chest wall too "heavy" to lift when attempting to breathe. (7) Overheating by atmospheric friction during descent.—This can be avoided either by preliminary rocket braking, by having a "heat sink" between the ship's outer surface and the cabin, or by having a thick forward surface which is gradually "ablated" as it melts and is not entirely destroyed by the time deceleration stops. In outer space heat received from the sunlit side can, by suitable adjustments, be radiated away to space on the opposite side. (8) Decompression due to leakage of air through the cabin wall from structural defect or holing by a meteorite.—Astronauts have hitherto worn pressure suits throughout the voyage as a precaution, but pressurized cabins in high-altitude aeroplanes are sometimes furnished with "pressure bags" into which the crew can plunge in an emergency.

Some of the physiological lessons learned from Major H. S. Titov's twenty-five-hour space flight were discussed in a leading article in a recent issue of the *Journal* (August 26, p. 573).

Prophylactics for the Maldives

Q.—*Two of my patients are going to the Maldive Islands as teachers. (1) What is the best insect repellent they can take with them? (2) What is the best malarial prophylactic for them to take? (3) What is Maldive fever, and is there any drug which prevents it?*

A.—Probably the best insect repellent at present on the market is "flypel," which contains diethyltoluamide. It is long-lasting, pleasant to use, and is dispensed in a vanishing-cream base. Dimethylphthalate was shown in the second world war to be very effective, but is an oily liquid and is less pleasant to use than flypel.

For malarial prophylaxis there is little to choose between chloroquine in doses of 300 mg. base weekly, pyrimethamine ("daraprim") 25 mg. weekly, and proguanil ("paludrine") in doses of 100 mg. daily. There are advantages in administering a malarial prophylactic daily, for if a dose of a prophylactic taken weekly is omitted an interval as long as the incubation period of malaria may elapse between doses and the disease may be contracted.

In a great number of places fevers contracted locally are known by a local geographic designation—e.g., Maldive fever. Often a number of different entities are referred to under the one designation. In other instances either dengue, sandfly fever, or malaria is the cause. The prevention is dependent upon primary identification of the causes of the fever.

Amphetamine Poisoning

Q.—*What are the signs, symptoms, and treatment of dexamphetamine poisoning? What directions for first-aid measures pending the doctor's arrival could be given?*

A.—The toxicity of the amphetamines is relatively low, and dexamphetamine is probably the safest of them. In comparison with many drugs in common use the margin of safety between a therapeutic dose and one which will produce toxic effects is wide; as much as 200 mg. of amphetamine has been taken in a day without any serious effects. The most common acute toxic effects are restlessness, hyperexcitability, dizziness, tremor, and irritability. Tachycardia is usually present, the patient may complain of angina, and circulatory collapse can occur. Sometimes confusion, delirium, and hallucinations are noted. Recently attention has been drawn to hyperpyrexia as an important manifestation of amphetamine poisoning.[1] The clinical picture is sometimes confused because the patient has taken an overdose of a preparation in which amphetamine is combined with some other drug such as a barbiturate.

The treatment of amphetamine poisoning is purely symptomatic; there is no specific antidote. If the patient is seen within an hour or two of taking the drug the stomach should be washed out. As a first-aid remedy the administration of flour and milk is recommended. The patient should be kept as quiet as possible and sedation with a fairly rapidly acting barbiturate such as amylobarbitone or perhaps with chlorpromazine is desirable. If the patient is very excitable and restless it may be necessary to give an intravenous barbiturate. The patient's temperature should be taken frequently, and if it shows a tendency to rise more than a few degrees measures to lower it, such as cold sponging, the application of sheets wrung out in cold water, and the use of a fan should be adopted.

Reference

1 Jordan, S. C., and Hampson, F., *Brit. med. J.*, 1960, 2, 844.

B.C.G. Vaccination

Q.—*B.C.G. vaccination is recommended at the age of 13, as this is supposed to be the age group most vulnerable to infection. At some schools the leaving age is 17 or 18. In these cases would it be better to postpone vaccination until, say, 15 to 16 years of age?*

A.—It is not desirable to postpone B.C.G. vaccination at the age of 13 years. The tendency now is to give B.C.G. somewhat earlier, and the Ministry of Health has recently[1] suggested that in many circumstances 10 to 11 years would be preferable. The age of 13 years was originally chosen because it was hoped to protect adolescents and young adults shortly before they left school. By this age, however, many have become tuberculin-sensitive and are therefore ineligible for vaccination. More is now known about the duration of immunity conferred by B.C.G. The fear that by giving the vaccine earlier the protection might not last until the school-leaving age has not been substantiated: B.C.G. may in fact protect for at least 7½ years and probably for a longer period. By vaccinating at 10 years protection may be expected during puberty and early adolescence—a dangerous time to receive a first infection.

Reference

1 *Brit. med. J.*, 1961, 2, 763.

Mixing of Antigens

Q.—*Since the addition of tetanus toxoid to diphtheria-pertussis antigen results in a lower titre of antibody to diphtheria, and since the spacing of tetanus toxoid is approximately the same as polio vaccine, is there any reason why these two latter should not be given simultaneously either by mixing them in the syringe or by using a ready-mixed antigen if one became available?*

A.—It is an incorrect assumption that the response to the diphtheria constituent of triple antigen is always depressed by mixing the antigens. Overloading a combined prophylactic with one component might lead to poor responses to the other components but immunologists aim at balanced mixtures to reduce this risk. Moreover, the pertussis vaccine constituent of triple vaccine functions as an adjuvant, analogous to alum in diphtheria vaccine A.P.T. or mineral oil in certain viral vaccines, and this improves responses.

Since there is a risk of interference from maternally transmitted antibodies poliomyelitis vaccine (Salk-type) should not be used until the baby is at least 6 months old. However, around the age of 18 months it can be given at the same session as DTP/Vac and at different inoculation sites, as suggested in the recent schedules of the Ministry of Health.[1] Quadruple vaccines are now under investigation in various countries: proper balance of the constituents is again important. On no account must a doctor make his own mixtures since there may be incompatibility of preservatives, etc., leading to poor responses.

Reference

[1] *Brit. med. J.*, 1961, 2, 763.

Polio Immunization in Patients with Porphyrinuria

Q.—*A woman aged 30, who was treated five years ago for tuberculous endometritis, was found to be suffering from porphyrinuria. Although she was sensitive to streptomycin we succeeded in desensitizing her and gave her a full course, and she is now symptom-free. However, she has been kept off drugs as much as possible, especially phenobarbitone, and has had no exacerbation of her porphyrinuria. She now asks whether it is safe for her to be immunized against poliomyelitis and what drugs she may take for headaches. Is porphyrinuria a contraindication to any form of immunization, and which are the safest analgesics, and, for that matter, antibiotics?*

A.—This problem has fortunately arisen already, and we have advised patients with acute intermittent porphyria that it is safe to be immunized against poliomyelitis. So far no trouble has been reported, so it is most likely that the situation is quite harmless, nor is there any published literature reporting dangers from any other form of immunization.

All the common analgesics such as acetylsalicylic acid, phenacetin, and codeine are harmless. Likewise most antibiotics are known to be harmless, although we usually try to avoid sulphonamides if possible as there are some suspicions that these have proved toxic. There is no doubt whatever about the severe dangers in taking phenobarbitone and any other drugs chemically related to phenobarbitone and, of course, mixtures of drugs sold under thousands of different names which contain some phenobarbitone.

Benign Metastasizing Haemangioma

Q.—*A man in his late thirties has been diagnosed as suffering from benign metastasizing haemangiomata. One of the discoloured swellings, which have occurred almost entirely on the upper extremities, has been removed and the pathologist's report stated that the condition was benign. What is the prognosis in such a case as this?*

A.—With no indication of the clinical or pathological features in this patient it is not possible to offer a very confident opinion. There is a condition described as metastasizing haemangioma, but it is exceedingly rare and I have never seen it. The histopathology is said to appear to be benign, but the course of the disease is that of malignant disease which may end fatally. It would seem that the patient described is very unlikely to be suffering from this disease but rather from some benign affection such as cherry angiomata (de Morgan spots), which can appear in showers and assume variable forms, or from pericytomata, which similarly shower and have a similar appearance, or from infective haemangiomata. All of these are benign affections. Glomus tumours may also be multiple and arise at this age. A good deal more information is necessary to allow any firm opinion.

NOTES AND COMMENTS

Ergometrine or Oxytocin?—Mr. H. Vincent Corbett (Liverpool) writes: May I be allowed, from personal experience, to add very briefly to your expert's reply ("Any Questions?" September 23, p. 841)? A good many years ago, on one occasion, for I never repeated it, I deliberately gave an intravenous injection of ¼ ml. or 1 ml. of pituitrin at the end of the second stage of labour; my memory fails me as to the exact dose, and I do not think "pitocin" was used. As long as I continue to practise obstetrics I shall never forget the rapidity of onset and severity of the resultant shock. Fortunately for the patient (and for me) she recovered. My advice to the questioner, for what it is worth, is that he should discard that of the authorities on the point he mentions. From additional and less harrowing experience gained at that time I always got the impression that pituitrin was in general superior to ergometrine, but for most occasions the latter seems amply to suffice, and even when in 1948 Mr. G. W. Theobald gave an old drug a new look its potentiality for evil was not wholly dispelled.

Our Expert replies: On one point at least Mr. Corbett and I are not really in conflict. His unfortunate experience of years ago merely serves to emphasize what I said about the risk of "pituitary shock"—namely, that the catastrophes mostly occurred with the old pituitrin and that usually the dose was excessive. A dose of ¼–1 ml. (5–10 units) of pituitrin should never be given intravenously; for a single administration the intramuscular route should always be chosen. In reaffirming that pitocin (and, of course, synthetic oxytocin) "is considered much safer" than pituitrin by the majority of obstetricians I can hardly do better now than refer the questioner to Mr. T. F. Corkill's recent letter (*Journal*, September 23, p. 826). His favourable comments on the use of the newer pituitary preparations are based on a very extensive experience indeed.

Correction.—Mr. G. A. Bagot Walters (Lincoln) writes: In my paper on "An Everyday Cystoscope" (September 23, p. 824) the size of the cystoscope sheath is given correctly as 21 Charrière, while the sizes mentioned for electrodes and catheter have been given as 5 and 7 Béniqué. These should also, of course, have been *Charrière*.

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